PALLADIUM-CATALYZED DIFUNCTIONALIZATION REACTIONS OF ETHYLENE AND DIENES

by

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ABSTRACT

During the past few decades, one-pot multicomponent reactions have attracted significant attention because of their ability to install multiple carbon-carbon or carbon-heteroatom bonds in a single step. However, the development of these reactions is a challenge because of the generation of many side products arising from undesired reaction pathways. Hence, optimization for the formation of desired products is difficult. Our group has been involved in developing such multicomponent reactions that take advantage of the stability of π-allyl/benzyl palladium species to generate biologically relevant and synthetically challenging products in an efficient manner. Herein, I describe the development of three novel multicomponent transformations to achieve difunctionalization of cheap olefins such as ethylene and dienes.

First, a Pd(II)-catalyzed three-component coupling involving ethylene, alkenyl triflates, and aryl boronic acids is described, where 1,1-vinylarylated products can be obtained in high yields and good to high selectivity. The crucial factor for an efficient reaction is cationic Pd(II)-intermediates, which prevent side products such as Suzuki products and Heck products. In general, the scope of the reaction is good as both electron-rich and electron-withdrawing boronic acids are tolerated. Heteroaromatic cross-coupling partners are also compatible under the reaction conditions. However, the scope is limited to six-membered alkenyl electrophiles, which bias the selectivity towards the formation of 1,1-vinylarylated products.

Second, the scope of this three-component reaction was extended to aryl electrophiles such as aryl diazonium salts. The reaction can also be used to couple allylic carbonates as the olefin source instead of ethylene to afford a wider range of 1,1-diarylalkanes. Also, deuterium labeling study and cross-over experiment revealed useful information regarding the mechanistic aspect of the reaction.

Finally, 1,2-hydrovinylation of terminal 1,3-dienes was achieved with alkenyl triflates/nonaflates and a hydride source. The reaction can be used to couple a variety of triflates derived from natural products to generate complex molecules in a mild fashion. Additionally, configurationally-defined alkenyl triflates (*i.e.*, *E/Z*) can be coupled efficiently to generate synthetically useful tri- and tetrasubstituted alkenes.

Dedicated to my family

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LIST OF ABBREVIATIONS

3 Å MS	three angstrom molecular sieves
μM	micromolar
Ac	acetyl
AcOH	acetic acid
Ac_2O	acetic anhydride
atm	atmosphere
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
BQ	benzoquinone
BuLi	butyllithium
calcd.	calculated
cat.	catalytic
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
cm	centimeters
cod	cyclooctadiene
dba	dibenzylideneacetone
DCE	1,2-dichloroethane

DIBAL-H	diisobutylaluminium hydride
DMA	*N*,*N*-dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
dr	diastereomeric ratio
EC_{50}	half maximum effective concentration
ee	enantioselectivity
equiv	equivalent
er	enantiomeric ratio
ESI	electron spray ionization
EtOAc	ethyl acetate
Et_2O	diethylether
Et_3N	triethylamine
FT	fourier transform
h	hour
Hz	hertz
IC_{50}	half maximum inhibitory concentration
IPA	isopropanol
IR	infrared
M	molar
MeCN	acetonitrile
MeOH	methanol
mg	milligrams

MHz	megahertz
mL	milliliters
mmol	millimoles
Ms	mesityl
MTBE	methyl *tert*-butyl ether
m/z	mass to charge ratio
NFSI	*N*-fluorobenzenesulfonimide
nm	nanomolar
NMR	nuclear magnetic resonance
o	ortho
obsd.	observed
OTf	trifluoromethanesulfonate
OTs	*para*-toluenesulfonate
Ph	phenyl
PhMe	toluene
ppm	parts per million
R_f	retention factor
rt	room temperature
TBDMS	*tert*-butyldimethylsilyl ether
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
Tert	tertiary
TFA	trifluoroacetate
THF	tetrahydrofuran

TOF	time of flight
wt%	weight percent

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CHAPTER 1

RECENT DEVELOPMENT IN THE TRANSITION-METAL-CATALYZED CARBON-CARBON BOND FORMING REACTIONS OF OLEFINS

Introduction

The use of transition-metal-catalysts, mainly Pd, Ni, Rh, and Ru for C–C bond formation, have a significant impact on chemist's approach towards the synthesis of natural products, pharmaceuticals, and materials.[1-6] Over the decades, these transition-metals have been widely explored for alkene functionalization reactions, because of their ability to undergo coordination with alkenes, thus activating them towards nucleophilic attack, cycloaddition or migratory insertion.[7,8] This chapter describes several of the important transition-metal-catalyzed C–C bond forming transformations of feedstock olefins such as ethylene and related dienes.

Ethylene as a Feedstock Olefin

Reactions of carbon feedstocks such as CO, CO_2 and simple olefins continue to garner the interest of synthetic and industrial chemists because of their abundance, as well as the significant consumption of consumer products obtained from them.[9,10] Ethylene is

one of the most important feedstock olefins, as it is the highest volume organic molecule produced in the world. In 2012, worldwide ethylene production was 156 million tons.[11] Generally, it is produced by steam cracking of hydrocarbons, which can be further obtained from fossil fuels. A significant amount of ethane found in shale gas reserves can also be cracked readily to afford ethylene. Dehydration of ethanol, obtained from fermentation of renewable sources such as glucose and starch, constitute an important step towards the green production of ethylene. In fact, a Brazil based petrochemical company "*Braskem"* has used this bio-renewable approach for the production of ethylene, which in turn is used to produce 200,000 tons of polyethylene per annum.[12,13] Although, in the recent past, numerous alternative approaches have been developed by researchers to produce green ethylene to reduce the dependency on nonrenewable resources and greenhouse gas emission, steam cracking of petrochemicals remains the most economically viable approach for the ethylene production. These new processes are far from being applied on practical scales, because of the cost and technological challenges associated with their bulk production.[14]

The market size of ethylene is attributed to the blooming demand in the commercial sector, as well as in the scientific research. It is estimated that around 60% of the ethylene produced is used in the production of polymers, such as low density polyethylene (LDPE) and high density polyethylene (HDPE). Additionally, ethylene is used in the production of fine chemicals such as ethylene glycol, styrene, vinyl chloride, and acetaldehyde. Some of the key transformations of ethylene utilized in industry for polymer and fine chemical synthesis are shown in Figure 1.1.[15]

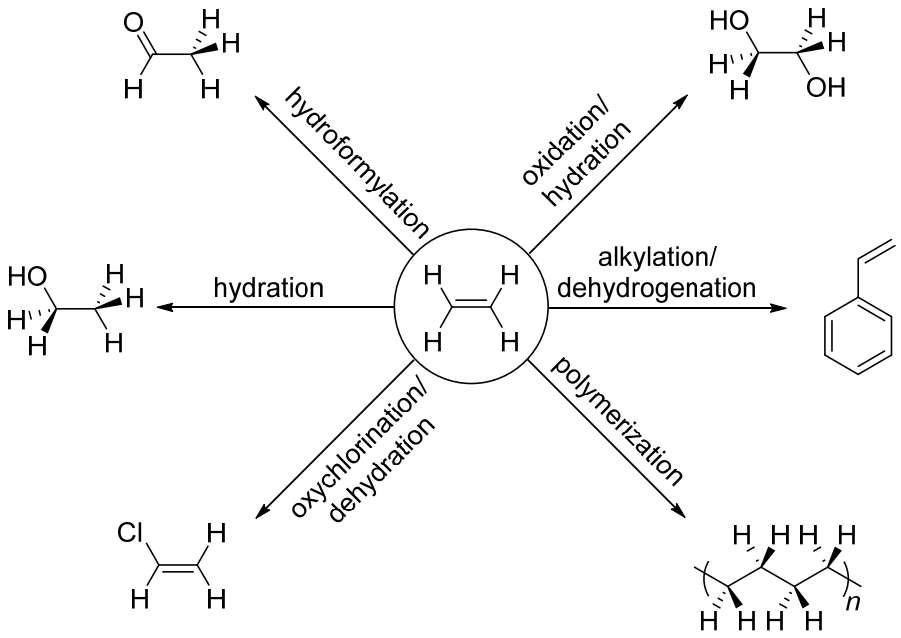


Figure 1.1. Industrial uses of ethylene.

Transition-Metal-Catalyzed C–C Bond Forming Reactions of Ethylene

Although significant advances have been achieved in the polymerization reactions of ethylene, its use in nonpolymeric synthetic method development and as a substrate in complex chemical synthesis is very rare, mainly because of the inherent simplicity associated with its structure. Moreover, the gaseous nature of ethylene further complicates efforts towards laboratory-scale reaction development. However, there are general examples of transition-metal-catalyzed ethylene functionalization reactions that lead to molecules of modest complexity.[16] One of these reactions is a Mizoroki-Heck reaction that involves the reaction of ethylene with aryl, vinyl, allyl or benzyl electrophiles to give terminal alkenes or dienes depending on the coupling partner. In 1971, the first report of Mizoroki-Heck reaction of ethylene with an aryl iodide was published by Mizoroki and co-workers (Figure 1.2a).[17] The reaction was catalytic in palladium but required elevated

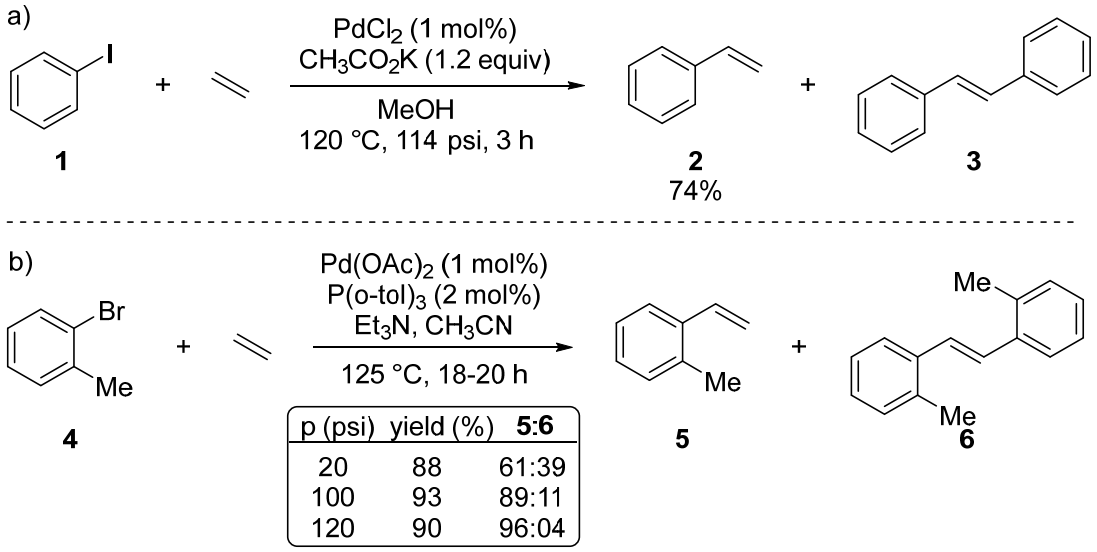


Figure 1.2. Mizoroki-Heck reaction. a) Mizoroki protocol, 1971. b) Heck protocol, 1978.

temperature and pressure for successful ethylene incorporation. Also, the formation of stilbene (**3**) formed by the reaction of the product (**2**) with **1** was another major drawback of the reaction. In 1978, Heck and co-workers tried to address the issue of stilbene formation by studying the effect of pressure of ethylene on product formation (Figure 1.2b).[18] It was observed that the formation of *ortho*-vinyltoluene (**5**) in the reaction between aryl bromide (**4**) and ethylene, was dependent on the pressure of ethylene, as increasing the pressure from 20 to 120 psi significantly suppressed the formation of stilbene side product (**6**).

Recently, nickel has been utilized to couple ethylene with more challenging sp^3 electrophiles. In 2010, Jamison and co-workers reported the first example of an intermolecular allylic substitution reaction of unbiased olefins such as ethylene using catalytic nickel under ambient temperature and pressure conditions (Figure 1.3).[19] Apart from the standard (*E*)-electrophile (**7a**), (*Z*)-allylic alcohol derivative (**7b**) gave

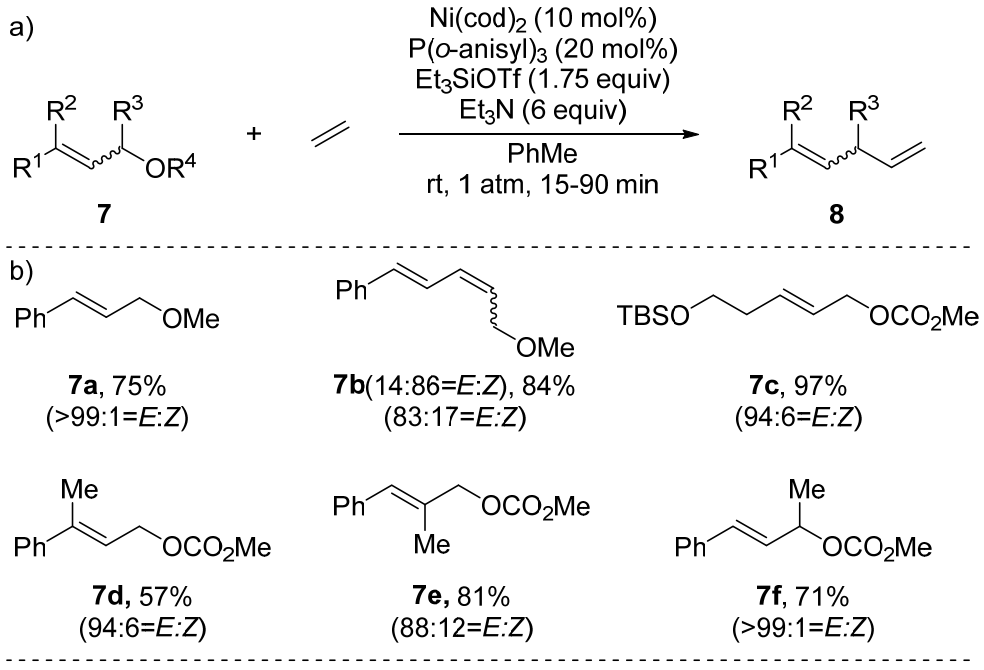


Figure 1.3. Nickel-catalyzed Mizoroki-Heck reaction of allylic electrophiles with ethylene. a) General reaction. b) Scope of the reaction.

predominantly (*E*)-product in excellent yield. Other representative examples are shown in Figure 1.3 (entries **7c**-**7f**) that showcase the highly stereoselective route to synthetically useful skipped dienes, which are prevalent in a wide variety of natural products and biologically active molecules.[20] The proposed mechanism for the formation of 1,4-dienes is shown in Figure 1.4. The initial oxidative addition of **7a** to Ni(0) leads to the formation of π-allylnickel species **A**. Then, triethylsilyl triflate undergoes ligand exchange with nickel in adduct **A**, which increases the electrophilicity of the metal center, hence facilitating ethylene binding to generate intermediate **B**. Migratory insertion leads to a relatively unstable Ni-alkyl species **C** that rapidly undergoes β-hydride elimination to form the product **8a** after catalyst dissociation from the diene intermediate **D**.

More recently, Jamison and co-workers have extended this method to include

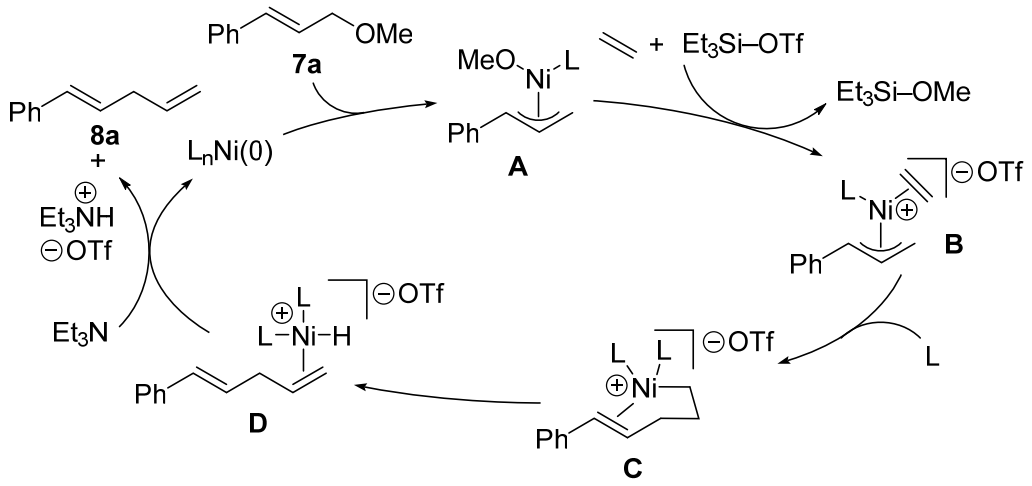


Figure 1.4. Proposed mechanism of the nickel-catalyzed Mizoroki-Heck reaction of allylic electrophiles with ethylene.

benzyl chloride derivatives as electrophiles under similar conditions (Figure 1.5).[21] The reaction is tolerant to both electron-rich and electron-withdrawing groups, as well as *ortho*-, *meta*- and *para*-substituted benzyl chlorides (entries **14a**-**14c**). Additionally, more challenging heteroatom containing substrates such as benzofuran (**14d**), benzothiophene (**14e**), and *N*-Boc-pyrrole (**14f**) gave excellent yields of the allyl benzene derivatives. The proposed mechanism is similar to that described in Figure 1.4, except the reaction is initiated by oxidative addition of benzyl chloride rather than the allyl ether or allyl carbonate.

In 2005, Jamison and co-workers reported a multicomponent coupling of ethylene with aldehydes and silyl triflates under Ni(0)-catalysis (Figure 1.6).[22,23] This reaction leads to synthetically useful allylic alcohol derivatives, starting from cheap and commercially available substrates. The reaction is well tolerated for nonenolizable and sterically hindered aldehydes (entries **16a**-**16d**). Mechanistically, the reaction proceeds via a [2+2] cycloaddition reaction of Ni(0) with ethylene and an aldehyde to form the 5-membered

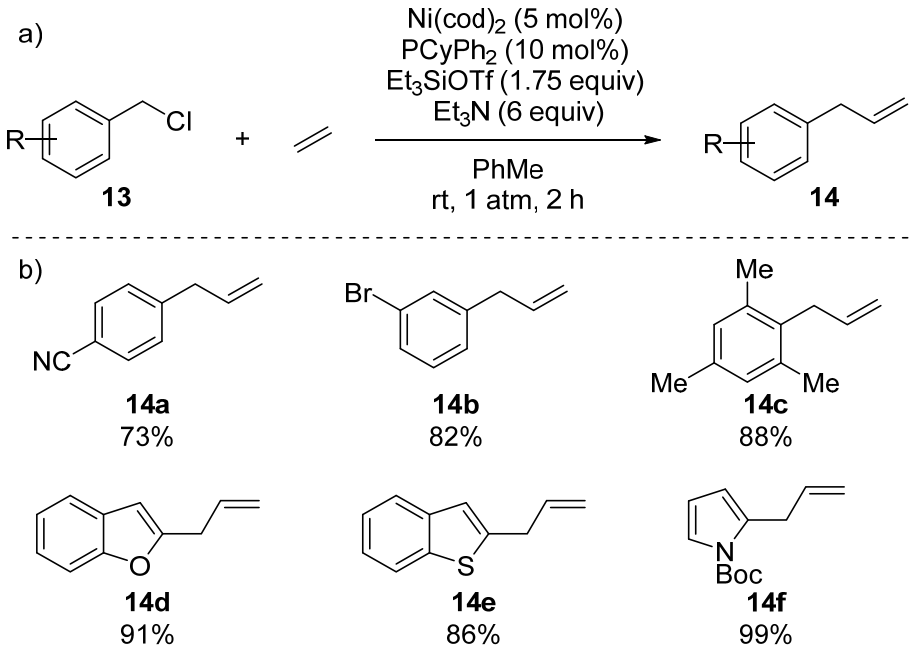


Figure 1.5. Nickel-catalyzed Mizoroki-Heck reaction of benzyl chlorides with ethylene. a) General reaction. b) Scope of the reaction.

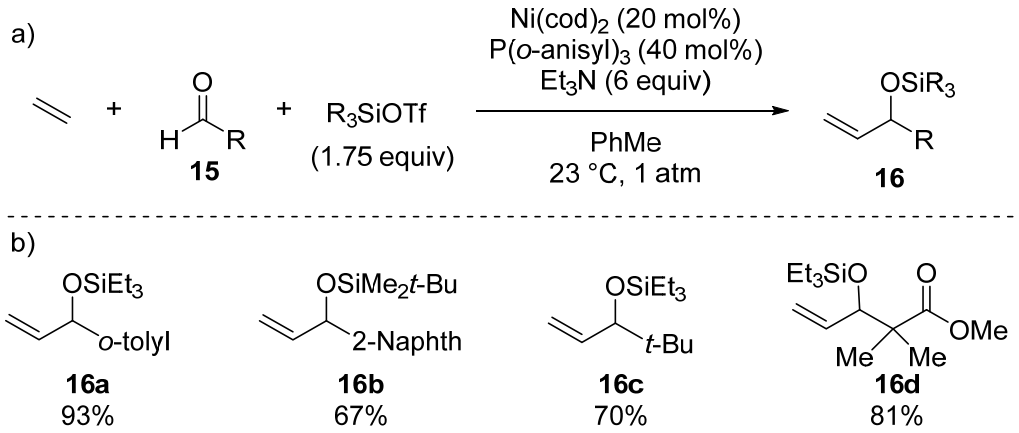


Figure 1.6. Nickel-catalyzed three-component oxidative coupling of ethylene with aldehydes and trialkyl silyl triflates. a) General reaction. b) Scope of the reaction.

oxametallacycle **A** (Figure 1.7). Then, silyl triflate facilitates the cleavage of the Ni–O bond, followed by β-hydride elimination to form the desired product (**16**).

Hydrovinylation of Olefins

Hydrovinylation reactions involve the addition of hydrogen and a vinyl group across the double bond of a biased alkene such as styrene or norbornene. This heterodimerization protocol is a very appealing strategy for the synthesis of precursors of 2-arylpropionic acids, which constitute an important class of nonsteroidal anti-inflammatory drugs (NSAIDs).[24] In 1972, Wilke and co-workers reported the first asymmetric hydrovinylation of ethylene with 1,3-cyclooctadiene using an allylnickel catalyst, a chiral phosphine ligand (**L1**), and a Lewis acid cocatalyst to give a skipped diene (**18**) with moderate enantioselectivity (Figure 1.8a).[25] A subsequent report showed that the hydrovinylation of norbornadiene (**19**) with ethylene under slightly different conditions gave 49% yield of the product (**20**) and 78% enantiomeric excess (Figure 1.8b).[26] Although, these protocols exhibited less than desired catalytic activity, this work was a milestone in the field of hydrovinylation, as it inspired other researchers to perform

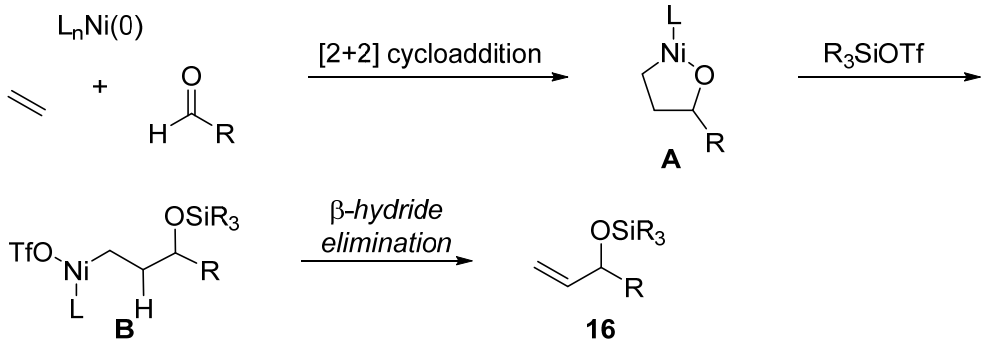


Figure 1.7. Mechanism of nickel-catalyzed three-component oxidative coupling of ethylene with aldehydes and trialkyl silyl triflates.

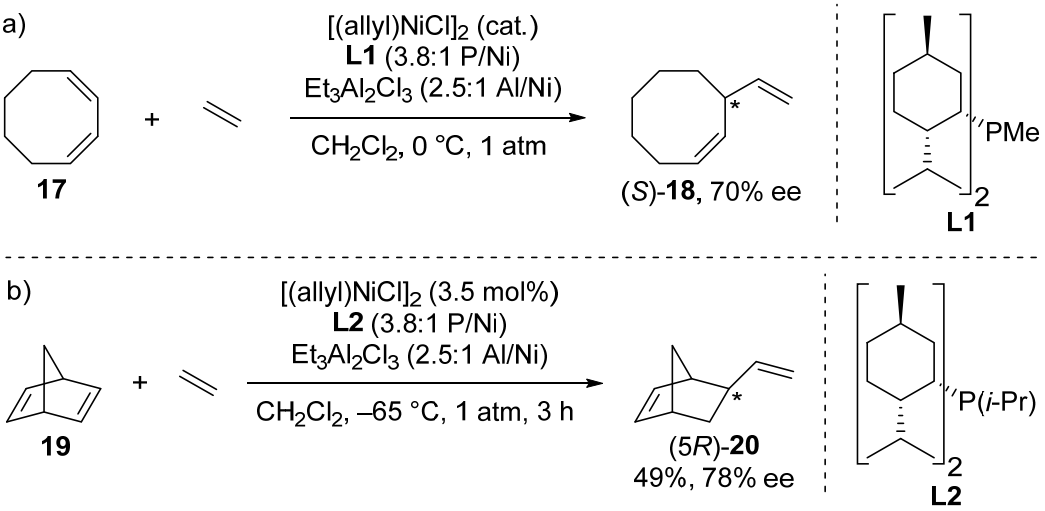
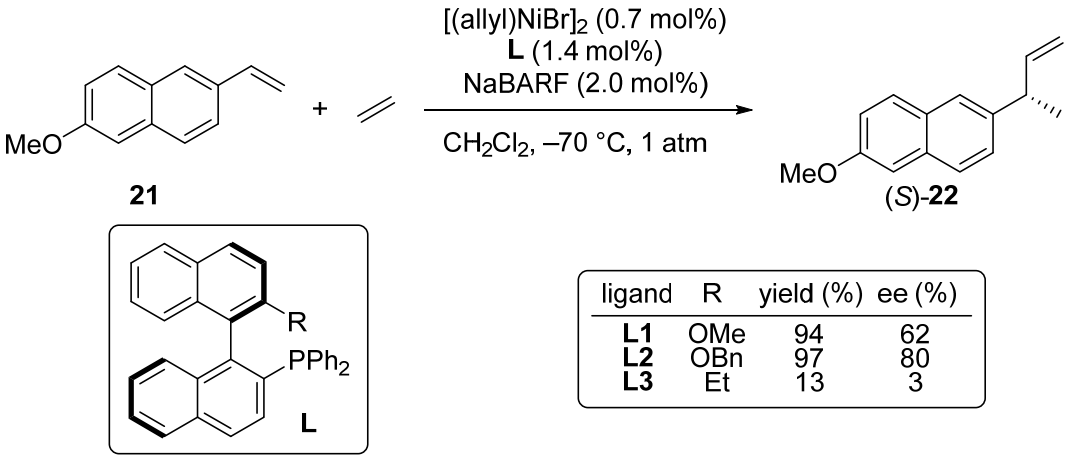


Figure 1.8. Nickel-catalyzed hydrovinylation reaction of biased dienes with ethylene. a) Reaction with 1,3-cyclooctadiene, 1972. b) Reaction with norbornadiene, 1973.

further studies that would address these shortcomings.

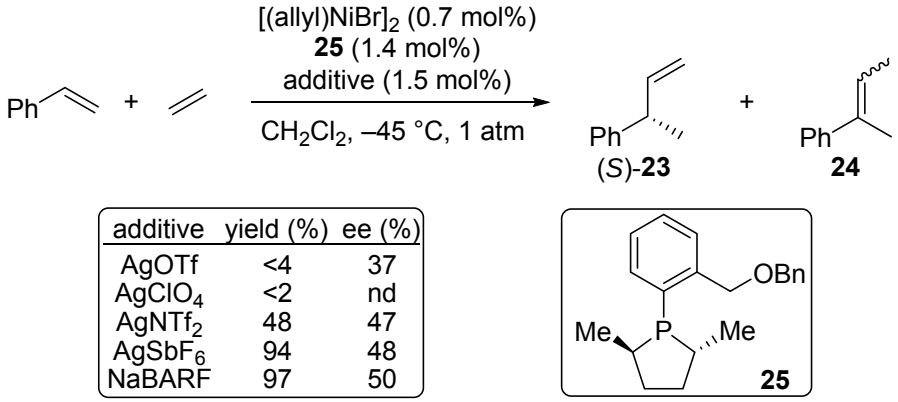
In 1998, Rajanbabu and co-workers reported the use of hemilabile-bidentate phosphine ligands (**L1**-**L3**) for asymmetric hydrovinylation of ethylene with 2-methoxy-6-vinylnapthalene (**21**) to form (*S*)-**22** in 97% yield and 80% ee, as shown in Figure 1.9.[27] The product obtained is a precursor for Naproxen, an anti-inflammatory drug. The presence of a hemilabile Lewis-basic functionality such as an ether group in the ligand is crucial for the efficiency of the reaction, as the use of a nonbasic group drastically impacted the catalyst activity and reaction selectivity.

Later, Rajanbabu and co-workers turned their attention towards hemilabile 1-aryl-2,5-dialkylphospholanes ligand (**25**) for the hydrovinylation of ethylene with styrene (Figure 1.10).[28] It was shown that the nature of the counterion plays a crucial role in determining the yield and enantioselectivity of the reaction. For example, the use of weakly coordinating counterions such as BARF and SbF_6^- gave excellent yields and



ligand	R	yield (%)	ee (%)
L1	OMe	94	62
L2	OBn	97	80
L3	Et	13	3

Figure 1.9. Nickel-catalyzed hydrovinylation reaction of styrene with ethylene using hemilabile bidentate phosphine ligands.



additive	yield (%)	ee (%)
AgOTf	<4	37
$AgClO_4$	<2	nd
$AgNTf_2$	48	47
$AgSbF_6$	94	48
NaBARF	97	50

Figure 1.10. Nickel-catalyzed hydrovinylation reaction of styrene with ethylene using 1-aryl-2,5-dialkylphospholane ligand.

moderate ee, whereas more strongly coordinating counterions such as $^{-}$OTf and ClO_4^{-} rendered the catalyst less effective. In 2009, extensive computational studies were undertaken by Jemmis and co-workers with the aim to investigate the mechanisticaspects of nickel/phospholane-catalyzed hydrovinylation reactions (Figure 1.11).[29] Initially, the nickel-precatalyst undergoes a series of ligand exchange reactions in the presence of a hemilabile phospholane ligand **25** to form ethylene bound cationic nickel species **A**.

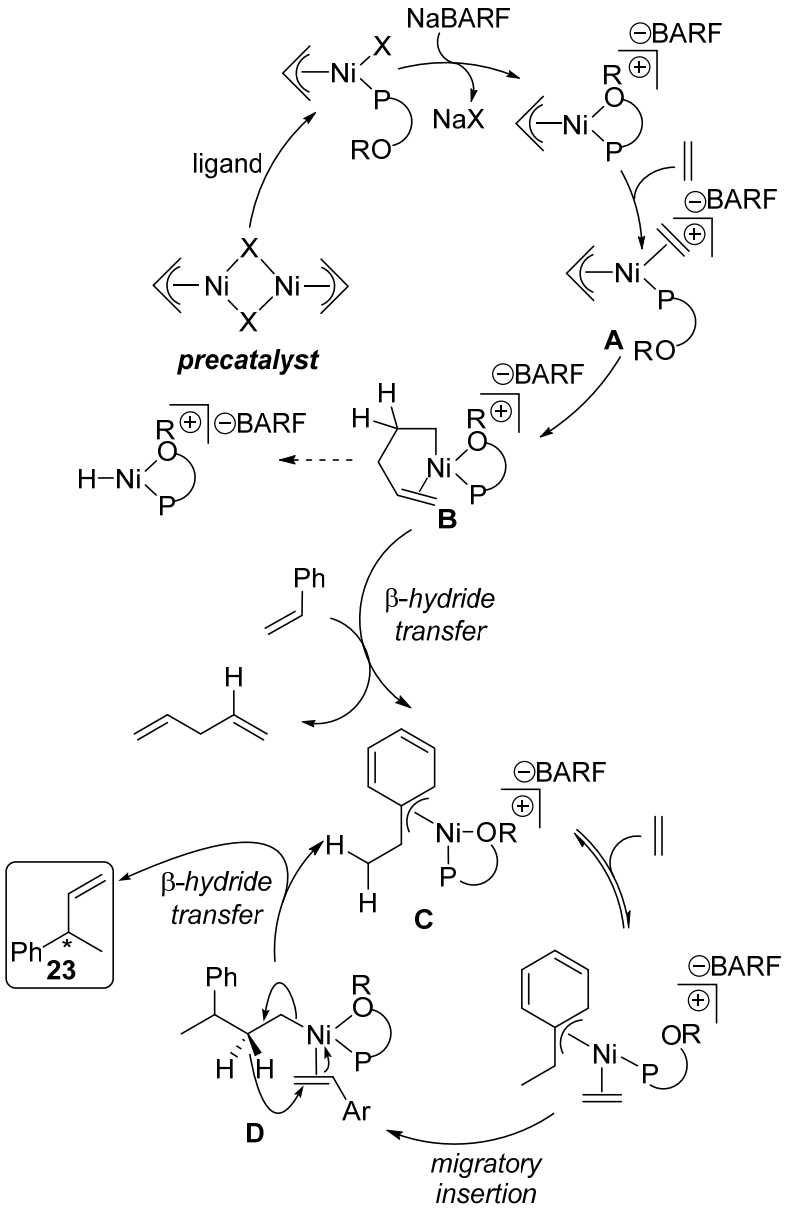


Figure 1.11. Proposed mechanism of the Ni-catalyzed hydrovinylation reaction of styrene with ethylene using 1-aryl-2,5-dialkylphospholane ligand.

Migratory insertion of ethylene leads to nickel-alkyl species **B**. The computational studies predicted that, at this stage the energy barrier to undergo β-hydride elimination is high, possibly due to the *trans*-orientation of the hydride and electron-rich phosphine around the nickel center. As a result this pathway is predicted to be prohibited, instead, the pathway involving direct hydride transfer from **B** to styrene is energetically favorable, leading to the formation of π-benzylnickel complex **C**. This is followed by ethylene coordination and migratory insertion to form intermediate **D**. Then, β-hydride elimination affords the desired hydrovinylation product **23** to complete the catalytic cycle. Interestingly, the isomerized side product **24** was not observed under the optimized reaction conditions, corroborating the computational studies that Ni–H is not generated in the reaction system. In 2012, a highly regio- and stereoselective 1,4-hydrovinylation of 1-vinylcycloalkenes was reported using a cobalt(II)-catalyst under ambient temperature and pressure conditions (Figure 1.12).[30] The reaction is highly selective for the formation of 1,4-hydrovinylation product (**27**) over the 1,2-hydrovinylation product (not shown). The use of different ring sizes as well as heteroatom containing cycloalkenes, coupled with ethylene gave the corresponding products in excellent yields and enantio- and regioselectivities (entries **27a**-**27d**).

Metathesis and Cycloaddition Reactions

Olefin metathesis reactions, particularly diene and ene-yne metathesis, are one of the most powerful bond construction approaches in modern organic synthesis.[6,31] The synthetic importance of these reactions is evident from the fact that the pioneers in this field were awarded the 2005 Nobel Prize in chemistry. Transition-metal-catalyzed olefin

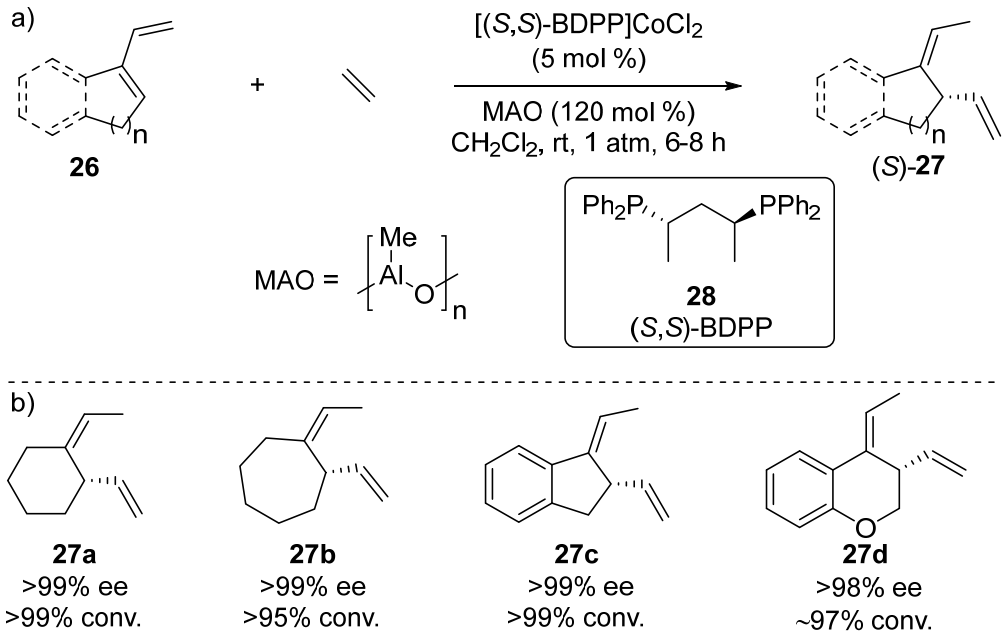


Figure 1.12. Cobalt-catalyzed 1,4-hydrovinylation reaction of cycloalkenes with ethylene. a) General reaction. b) Scope of the reaction.

metathesis involves the reaction between two unsaturated molecules, which undergo bond reorganization to form another set of unsaturated molecules, at least one of which is complex and precious. Ethylene can play a crucial role, both as a substrate, as well as facilitator, in these metathesis reactions.

In 1997, Mori and co-workers reported a ruthenium-catalyzed intermolecular enyne metathesis reaction between ethylene and various alkynes to form synthetically useful 1,3-dienes (Figure 1.13).[32,33] The overall transformation transfers the two methylene units of ethylene to the two sp-hybridized carbons of alkyne. The substrate scope was found to be broad and several functional groups such as ethers, esters, acetals, and tosyl-protected amines were well-tolerated (entries **30a**-**30e**). Mechanistically, the initial step involves the formation of an active catalyst **C** by the reaction between ruthenium alkylidene catalyst **31** and ethylene (Figure 1.14). Then, alkyne **29** undergoes a cycloaddition reaction with **C**,

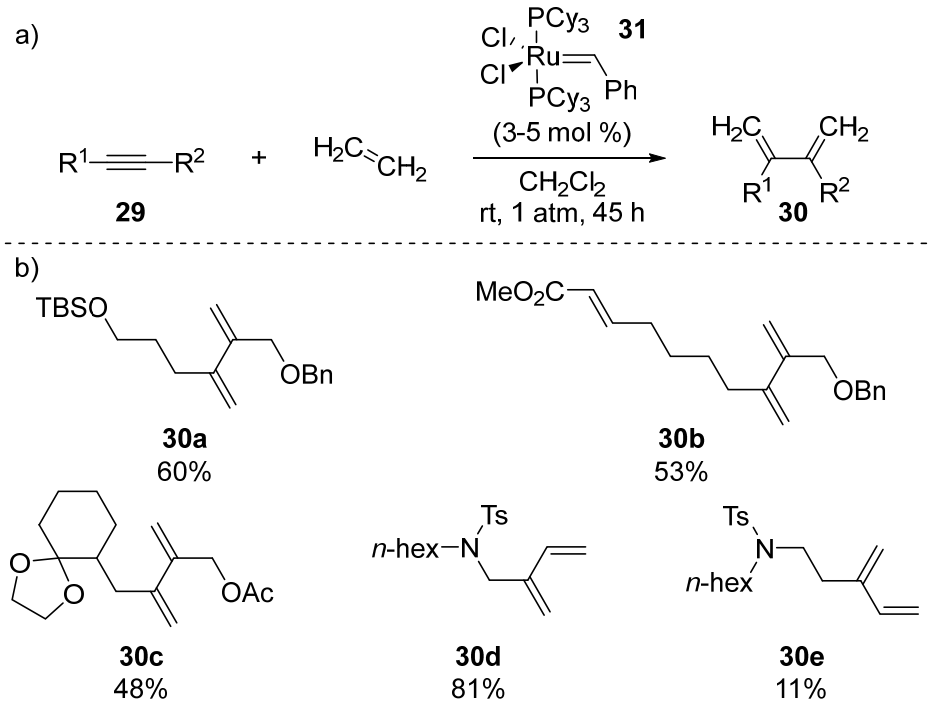


Figure 1.13. Ruthenium-catalyzed metathesis reaction of ethylene with alkynes to form 1,3-dienes. a) General reaction. b) Scope of the reaction.

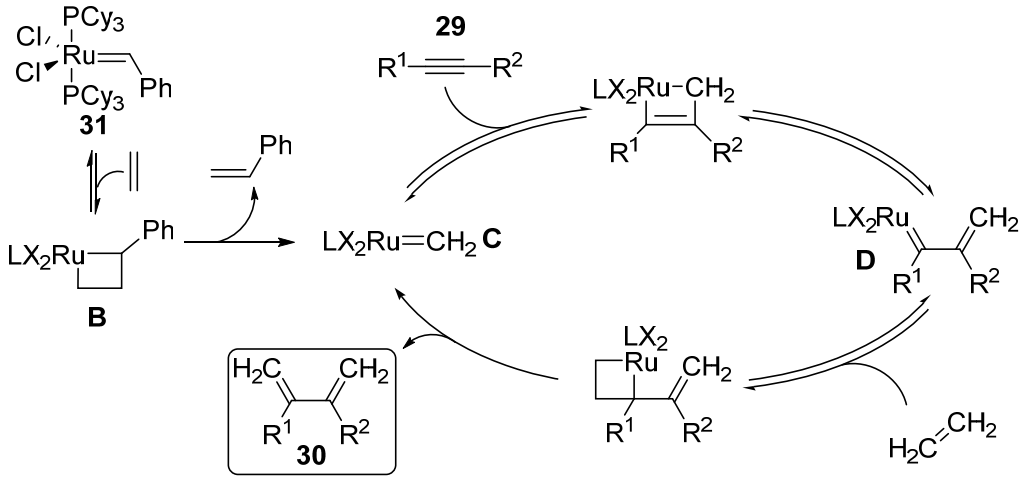


Figure 1.14. Proposed mechanism of the ruthenium-catalyzed metathesis reaction of ethylene with alkynes to form 1,3-dienes.

followed by bond reorganization to form intermediate **D**. Finally, a third cycloaddition/bond reorganization with ethylene affords the desired product **30** along with the regeneration of the active catalyst **C**.

In 2001, Mori and co-workers reported the tandem ring-opening and ring-closing metathesis of 1,6-cycloalkene-ynes under an ethylene atmosphere (Figure 1.15).[34] For example, the reaction of enyne **32** with ethylene in the presence of ruthenium-catalyst gave a 90% yield of triene **33**. Mechanistically, the important step involves the formation of ruthenacyclobutane intermediate **B**, which undergoes cycloreversion to form **C**, followed by another cycloaddition/cycloreversion with ethylene to generate the active catalyst **A** and triene **33**. In this work, ethylene has been utilized both as a substrate and as a facilitator, as the absence of ethylene afforded polymerized side products.

In 1998, Mori and co-workers reported the use of ethylene for an intramolecular ring-closing metathesis reaction (Figure 1.16).[35] For example, a dramatic increase in

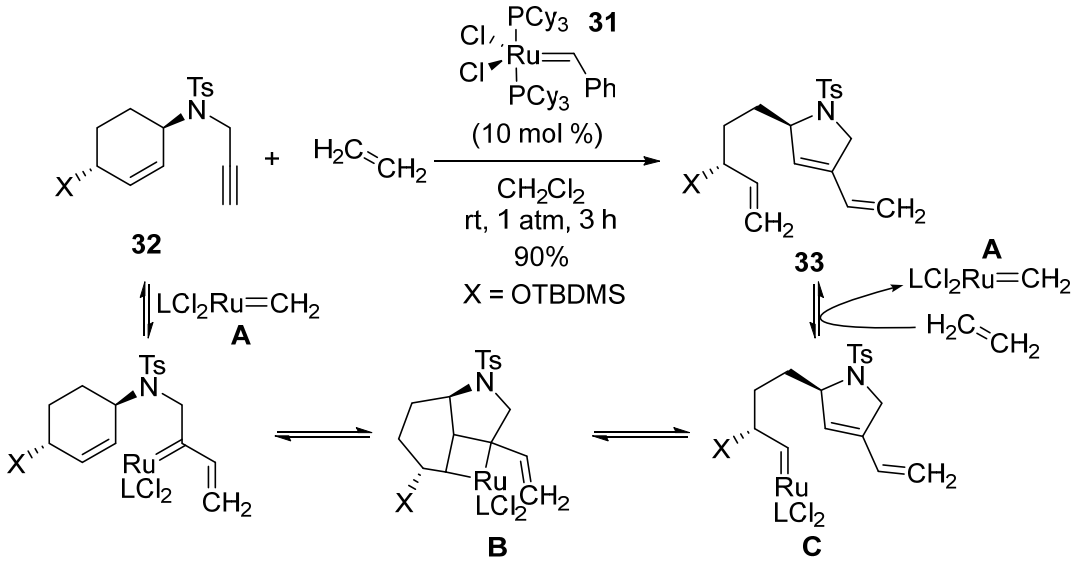


Figure 1.15. Proposed mechanism of the ruthenium-catalyzed metathesis reaction of ethylene with 1,6-enyne to form 1,3-diene.

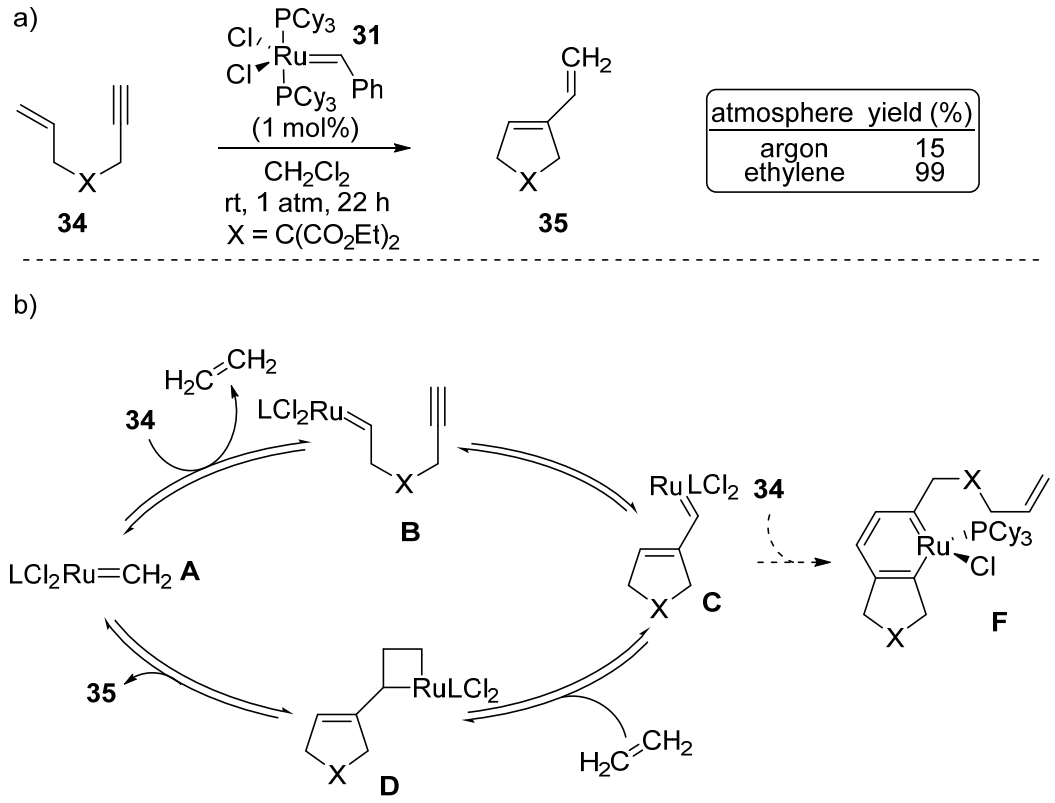


Figure 1.16. Generation of 1,3-dienes using ruthenium-catalyzed metathesis reaction of ethylene and cycloalkene-ynes. a) General reaction. b) Proposed mechanism.

reactivity towards the formation of diene **35** was observed, when enyne **34** was subjected to Grubbs 1st generation catalyst under an atmosphere of ethylene. In 2011, Fogg and co-workers provided mechanistic insight into the role of ethylene.[36] It was shown that ethylene played two major roles. 1) Generation of an active catalyst **A**, as described in Figure 1.14, along with the generation of the desired 1,3-diene product **35**. Low yield in the absence of ethylene was attributed to the formation of ruthenacycle **F** derived from the reaction of **C** with second equivalent of enyne **34**.

In 2001, Shair and co-workers applied the ethylene-promoted ring closing enyne metathesis to the synthesis of (–)-longithorone A (**38**, Figure 1.17).[38,39] This protocol

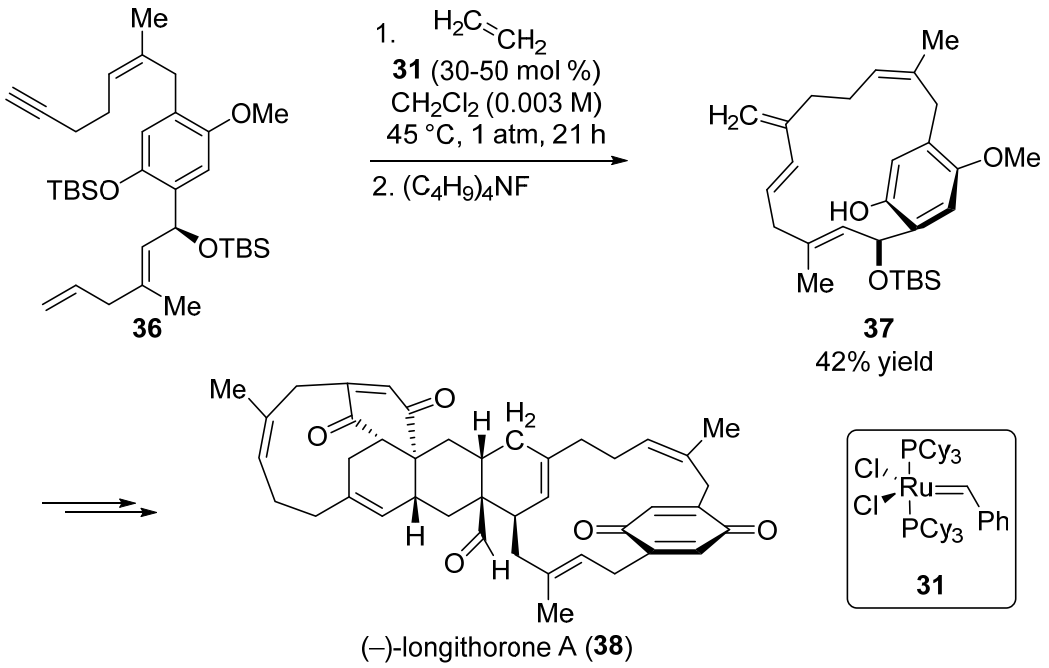


Figure 1.17. Use of enyne metathesis reaction in the total synthesis of (–)-longithorone A.

transforms enyne substrate **36** to a macrocyclic 1,3-diene **37** in 42% yield with greater than 25:1 atropdiastereo- and *E*/*Z*-selectivity.

Interestingly, the use of a non-alkylidene ruthenium catalyst instead of Grubbs's 1st generation catalyst in the reaction of 1,6-terminal enynes with ethylene gave completely different reactivity (Figure 1.18).[37] For example, enyne **34** undergoes alkenylative cyclization in the presence of ethylene to afford 85% yield of exocyclic diene **39**, whereas the metathesis product **35** was not observed at all. The formation of **39** can be explained by the initial formation of a ruthenacyclopentene intermediate **A** from oxidative cyclization, which undergoes ring expansion after migratory insertion of ethylene to form a ruthenacycloheptene **B**. Lastly, β-hydride elimination followed by reductive elimination leads to the exocyclic diene product **39**. This method was applied to the synthesis of a wide variety of 1,3-diene containing carbo- and heterocycles (entries **39a**-**39d**).

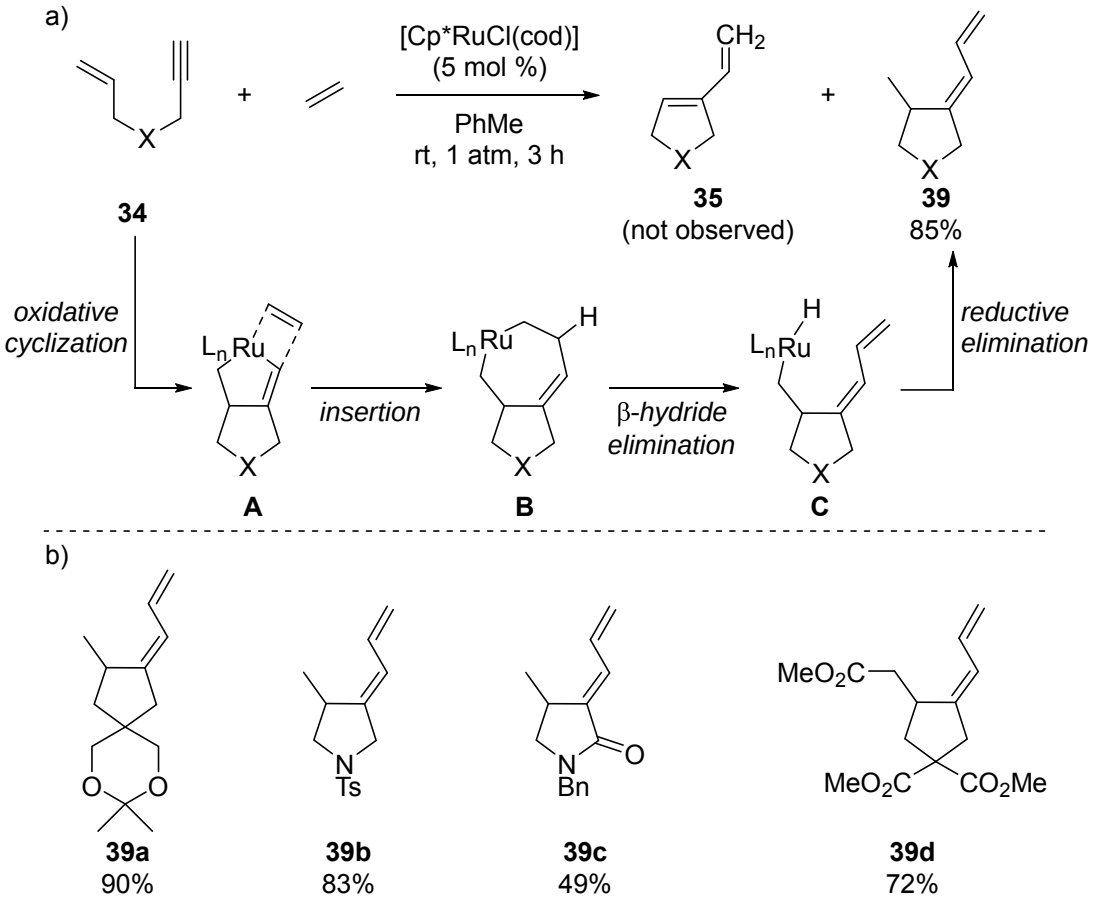


Figure 1.18. Generation of 1,3-dienes using ruthenium-catalyzed cycloaddition reaction of ethylene and cycloalkene-ynes. a) General reaction and mechanism. b) Additional examples.

Palladium-Catalyzed Difunctionalization Reactions of 1,3-Dienes

Apart from ethylene, other feedstock olefins such as terminal dienes have also been utilized for complex molecule synthesis using transition-metal-catalysis.[40,41] Their unique reactivity enables the synthesis of organic molecules in a rapid and atom-economical fashion. Therefore, for the past few decades significant efforts have been devoted to develop difunctionalization reactions of dienes. Palladium has become the metal of choice for olefin difunctionalization reactions because of its propensity to undergo coordination and subsequent migratory insertion to 1,3-dienes to form Pd-allyl species, which

presumably exist as π-allylpalladium intermediates (Figure 1.19).[41] Also, the formation of a π-allyl intermediate is one of the main factors for the success of these reactions, because it prevents the Pd-alkyl species from undergoing undesired pathways such as β-hydride elimination. This part of the chapter illustrates various ways to form and trap π-allylpalladium species, enabling the facile synthesis of difunctionalized products.

In 1980s and 1990s, Bäckvall and co-workers developed several difunctionalization reactions of dienes based on the stabilization of Pd(II)-alkyl intermediates.[42-45] One such example is a Pd(II)-catalyzed aminochlorination of a cyclic 1,3-diene (**40**) with *N*-Tosyl amine as an intramolecular nucleophile and LiCl as a chloride source (Figure 1.20a).[44] The reaction proceeds via coordination of Pd(II) to diene, followed by *anti*-aminopalladation to form a π-allylpalladium intermediate **A**. Subsequent attack of a chloride ion on the π-allyl complex led to **41** in excellent yield and selectivity. Following this transformation, numerous examples have been reported in the past two decades. For example, in 2005, Booker-Milburn and co-workers reported a Pd(II)-catalyzed 1,2-diamination of a diene **42** (Figure 1.20b).[46] The reaction proceeds via initial aminopalladation of **42** with *N*,*N*'-diethyl urea as a nucleophile to form π-allylpalladium intermediate **B**. Subsequent

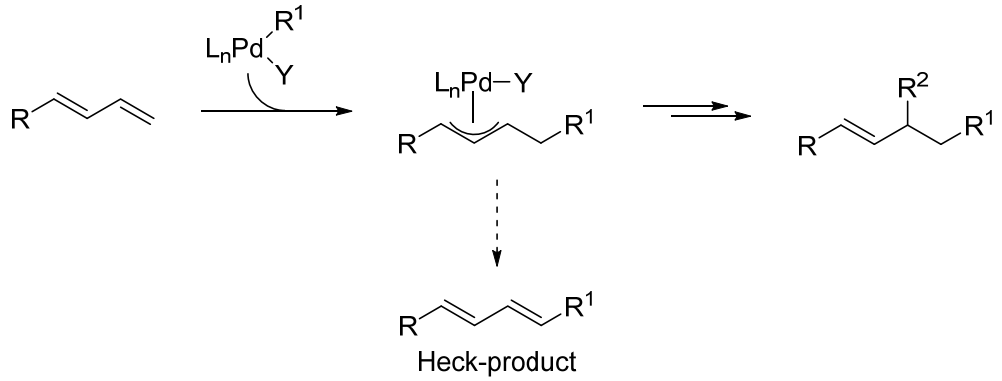


Figure 1.19. Formation and reactivity of π-allylpalladium complex.

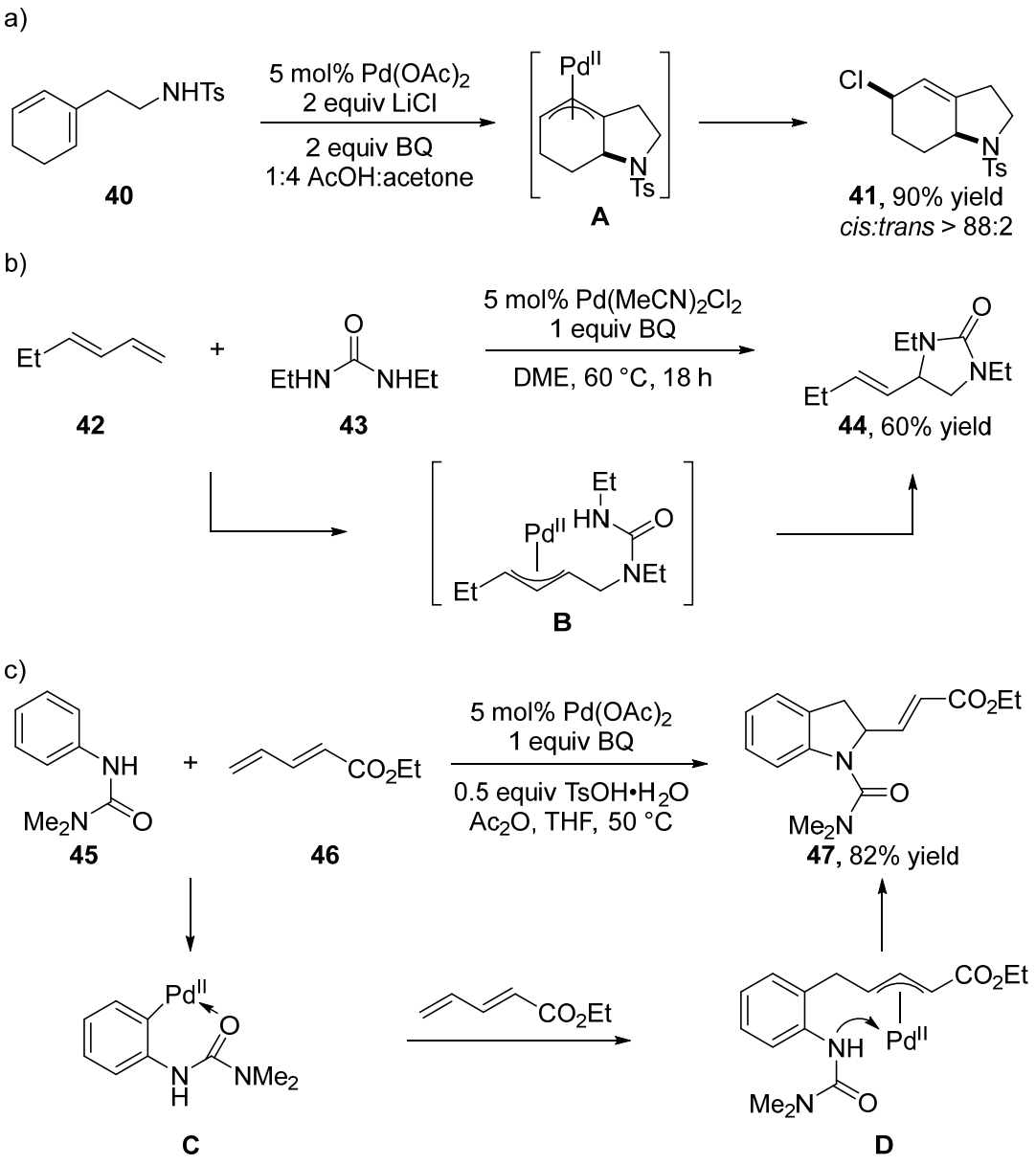


Figure 1.20. Pd(II)-catalyzed difunctionalization reactions of dienes. a) Aminochlorination of cyclic 1,3-dienes from Bäckvall and co-workers, 1990. b) Diamination of terminal 1,3-dienes from Booker-Milburn and co-workers, 2005. c) Tandem C–H activation followed by diene functionalization from Booker-Milburn and co-workers, 2008.

intramolecular attack by the tethered nucleophile would furnish **44** in 60% yield. In 2008, Booker-Milburn and co-workers reported a Pd(II)-catalyzed approach for tandem C–H activation followed by diene functionalization (Figure 1.20c).[47] In this report, functional group directed *ortho* C–H activation of **45** was achieved to form Pd(II)-aryl species **C**. Then, this undergoes migratory insertion into a diene **46**, followed by generation of a stable π-allylpalladium species **D**, which would furnish **47** in 82% yield via intramolecular attack by nitrogen of the urea molecule.

In 2010, Sigman and co-workers reported a Pd(II)-catalyzed hydroarylation of 1,3-dienes with boronic esters under oxidative conditions (Figure 1.21).[48] This protocol showcases a unique way of generating Pd–H by Pd(II)-initiated oxidation of isopropanol that transfers the hydride to Pd(II) along with the formation of acetone. The diene (**48**) then undergoes migratory insertion to the ligand bound Pd–H forming π-allylpalladium intermediate **A**. Lastly, **A** undergoes transmetallation with the boronic ester (**49**) followed by reductive elimination to form the 1,2-addition product selectively over the 1,4-addition product. To determine the origin of regioselectivity, apart from the phenyl containing substrate (**48**), various aliphatic 1,3-dienes were evaluated. As shown in entries **50b**-**50d**, the trend is the same in all cases yielding the 1,2-addition product in high yields and >20:1 site selectivities. This shows that both electronics as well as sterics on the diene can favor 1,2-hydroarylation products in high site-selectivity. Although this unique approach afforded the products in synthetically useful yields and selectivities, it suffers from the drawback of complex reaction conditions including an oxidative environment, high temperature and strong base (e.g. potassium *tert*-butoxide), which limits the scope of the reaction.

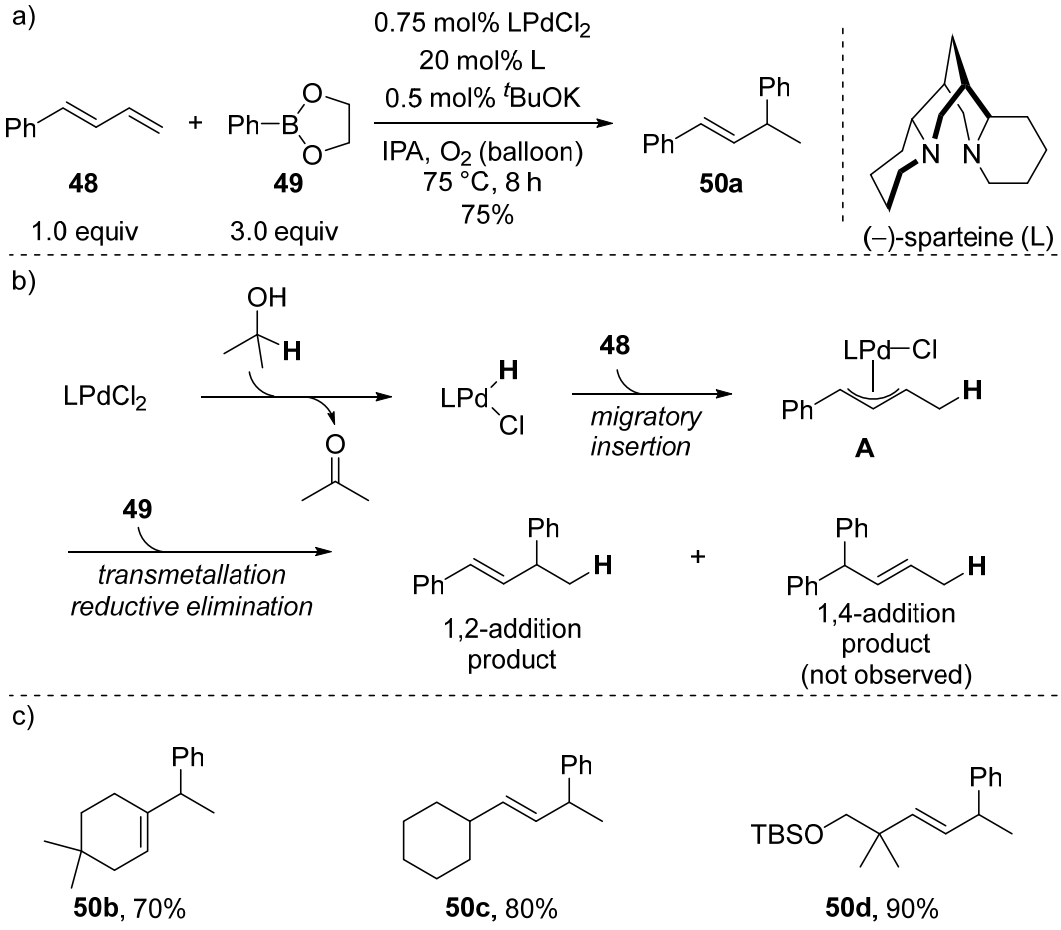


Figure 1.21. Palladium-catalyzed 1,2-hydroarylation of terminal 1,3-dienes. a) General reaction. b) Proposed mechanism. c) Selective examples.

In 2011, Sigman and co-workers reported a simpler approach for the difunctionalization of terminal 1,3-diene **48**, where the first step involves the oxidative addition of an enol triflate **51** to Pd(0) to form Pd-alkenyl intermediate **A** (Figure 1.22).[49] Migratory insertion of the diene leads to π-allyl/Pd intermediate **B**, which is presumably slow to undergo β-hydride elimination, thus preventing undesired pathways. It should be noted that the reactivity of the reaction was controlled by the careful design of the substrates. For example, the use of an enol triflate as an electrophile rendered the palladium electrophilic, which facilitated migratory insertion rather than direct reaction with aryl

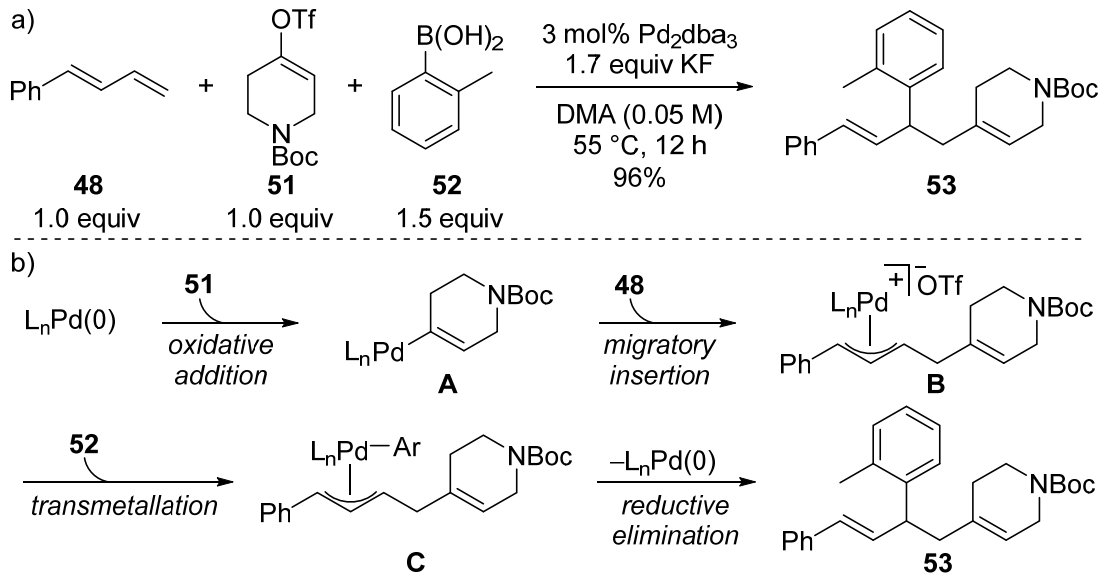


Figure 1.22. Palladium-catalyzed 1,2-vinylarylation of terminal 1,3-dienes. a) General reaction. b) Proposed mechanism.

boronic acid, thus preventing the formation of the Suzuki cross-coupled product (not shown). The intermediate **B**, then undergoes transmetallation followed by reductive elimination to complete the catalytic cycle. Since, reductive elimination is possible on either side of the π-allyl, formation of 1,2-difunctionalized product **53** is favored because of the steric and/or electronic effects as discussed in the above reaction.

Recently, this methodology was extended to include feedstock olefin such as 1,3-butadiene to achieve regioselective 1,4-difuctionalization over 1,2-difunctionalization.[20,50] As shown in Figure 1.23a, this methodology was used to synthesize skipped triene core of ripostatin A **56** in 71% yield and good regio- and stereoselectivity. In 2014, aryl diazonium salt was included as an electrophile that led to the selective installation of two different aryl groups on the terminal 1,3-diene **58** (Figure 1.23b).[51] The mechanism of the reaction is similar to that shown in Figure 1.22, except that the reaction is initiated by an aryl diazonium salt rather than an enol triflate. A chiral ligand (**L**) has also been identified that

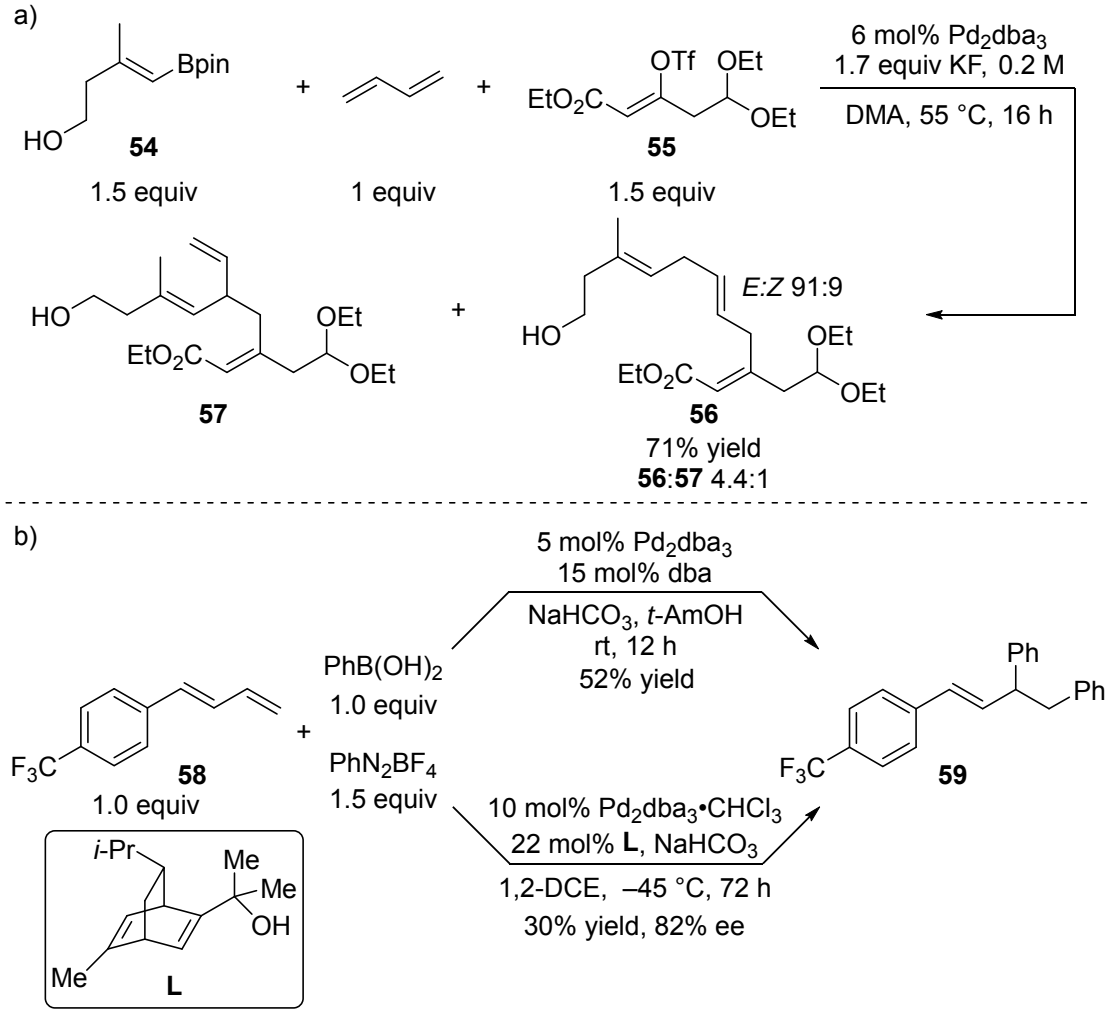


Figure 1.23. Palladium-catalyzed difunctionalization of dienes. a) 1,4-divinylation of butadiene. b) 1,2-diarylation of terminal 1,3-diene.

afforded the product **59** in 30% yield and 82% ee.

Conclusion

A major portion of this chapter has presented recent developments in the functionalization reactions of ethylene. The pioneering works of Rajanbabu et al. and others have had a substantial impact on the field of ethylene derivatization to form small molecules. However, the development of transition-metal-catalyzed difunctionalization reactions of ethylene to generate relatively complex molecular scaffold is still in its infancy. In the following two chapters, utilization of an electrophilic Pd(II)-complex for the 1,1-difunctionalization of ethylene by trapping of the π-allyl/benzylpalladium intermediate will be described.

This chapter has also presented difunctionalization reactions of 1,3-dienes, which has been achieved by initial formation of a stable π-allylpalladium intermediate followed by reaction with various nucleophiles. The unique stability of π-allylpalladium intermediates has been explored further to achieve 1,2-hydrovinylation of terminal 1,3-dienes to form synthetically useful tri- and tetrasubstituted alkenes in a highly regio- and stereoselective fashion. This approach is discussed in the fourth chapter.

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CHAPTER 2

DEVELOPMENT OF A PALLADIUM-CATALYZED 1,1-VINYLARYLATION REACTION OF ETHYLENE

Introduction

Since the discovery of palladium by Wollaston[1] in 1803, it has been widely employed in the electroplating of jewelry,[2] the generation of pharmaceuticals,[3] in photography[4] and most importantly in the present context, as a catalyst in organic synthesis.[5] Over the past few decades, it has been extensively used as a catalyst in a number of synthetic transformations including the Wacker oxidation,[6-9] cross-coupling reactions,[10] and the Heck reaction.[11,12] Although expensive, its unique properties serve as an attractive tool for carbon-carbon and carbon-heteroatom bond formation. For example, the palladium-catalyzed arylation and vinylation of olefins, pioneered independently by Heck and Mizoroki, has received considerable attention over the years, and these reactions have developed into a versatile C–C bond-forming processes, in both industrial and laboratory-scale synthesis.[5,11,12] Alkene difunctionalization is another palladium-mediated reaction, which leads to the formation of two new bonds across an alkene by the stabilization of Pd-alkyl intermediates.[13] The stabilization can be achieved mainly by three methods: a) use of a strong oxidant, which can facilitate faster oxidation of the palladium over β-hydride

elimination;[14] b) coordination of palladium with a heteroatom present in its vicinity, thus saturating its coordination sphere to prevent β-hydride elimination;[15] c) formation of a more stable π-allyl/benzylpalladium intermediate.[13] In this chapter, all three approaches will be briefly discussed.

Background

Recently, the use of high oxidation state palladium, *i.e.*, Pd(IV), has been explored extensively for carbon-carbon and carbon-heteroatom bond formation.[14,16,17] Pd(IV) is usually accessed by the use of a strong oxidant, which transforms a Pd(II)-alkyl to a Pd(IV)-alkyl species, thus preventing β-hydride elimination. Pd(IV) species also readily undergo reductive elimination, which could otherwise require forcing conditions. A general catalytic cycle involving a Pd(II)/Pd(IV) pathway is shown in Figure 2.1. The first step

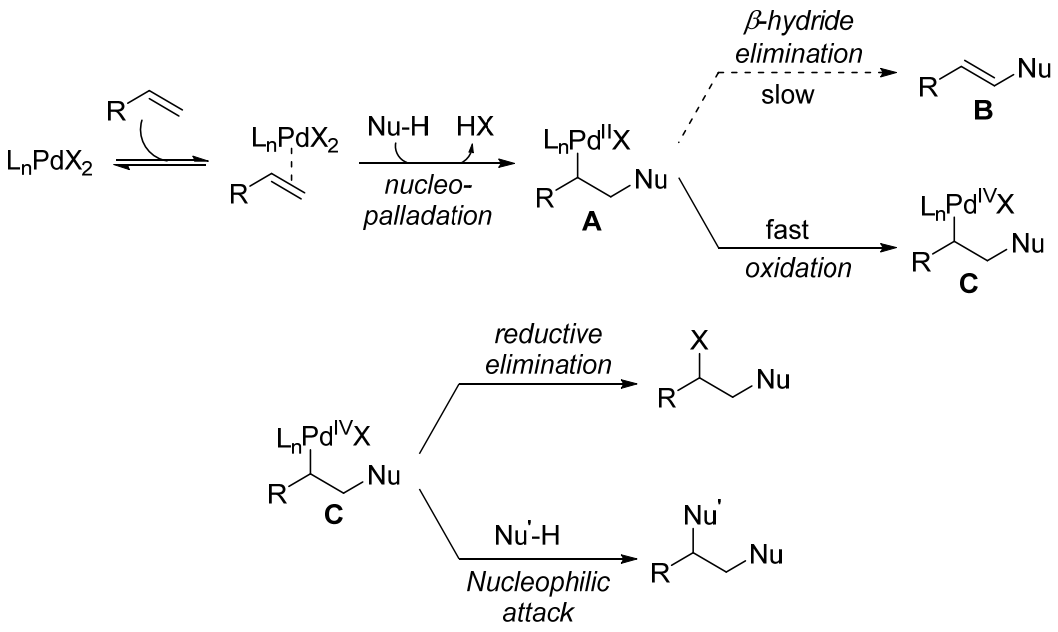


Figure 2.1. General mechanism of Pd(II)/Pd(IV) catalysis.

involves alkene coordination to Pd(II), thus activating it towards nucleopalladation. Attack of a nucleophile at the less hindered end of the alkene leads to the formation of a Pd(II)-alkyl intermediate **A**. This intermediate then undergoes oxidation faster than β-hydride elimination to form Pd(IV)-alkyl species **C**, which can either undergo reductive elimination or attack by an external nucleophile to form the corresponding difunctionalized product.

In 2005, Sorenson and co-workers reported a Pd(II)-catalyzed intramolecular aminoacetoxylation of alkenes.[18] A strong oxidant such as $PhI(OAc)_2$ was used to oxidize the Pd(II)-alkyl intermediate to form a Pd(IV)-alkyl species, which then undergoes reductive elimination to afford the corresponding product in a good yield (Figure 2.2a). Subsequently, Muñiz and co-workers reported an intramolecular diamination of terminal olefins substituted with a urea molecule under Pd(II)/Pd(IV) catalysis, leading to concomitant formation of fused rings (Figure 2.2b).[19-21] Soon after, Stahl and co-workers reported a Pd(II)-catalyzed intermolecular aminoacetoxylation of terminal alkenes using pthalimide as a nucleophile, and $PhI(OAc)_2$ both as an oxidant and an acetyl source (Figure 2.2c).[22] Similarly, Sanford and co-workers reported aminooxygenation of alkenols with a pthalimide to form 3-aminotetrahydrofurans in a highly diastereoselective fashion (Figure 2.2d).[23]

Recently, other oxidants such as *N*-fluorobenzenesulfonimide (NFSI) have been used effectively to oxidize Pd(II) to Pd(IV) intermediates. For example, in 2009, Micheal and co-workers reported a diamination of unbiased olefins in EtOAc using NFSI, which acts both as an oxidant and an aminating agent (Figure 2.3a).[24] However, the use of aromatic solvents under similar conditions led to electrophilic aromatic substitution of arenes after the initial formation of Pd(IV)-alkyl species to afford aminoarylation products

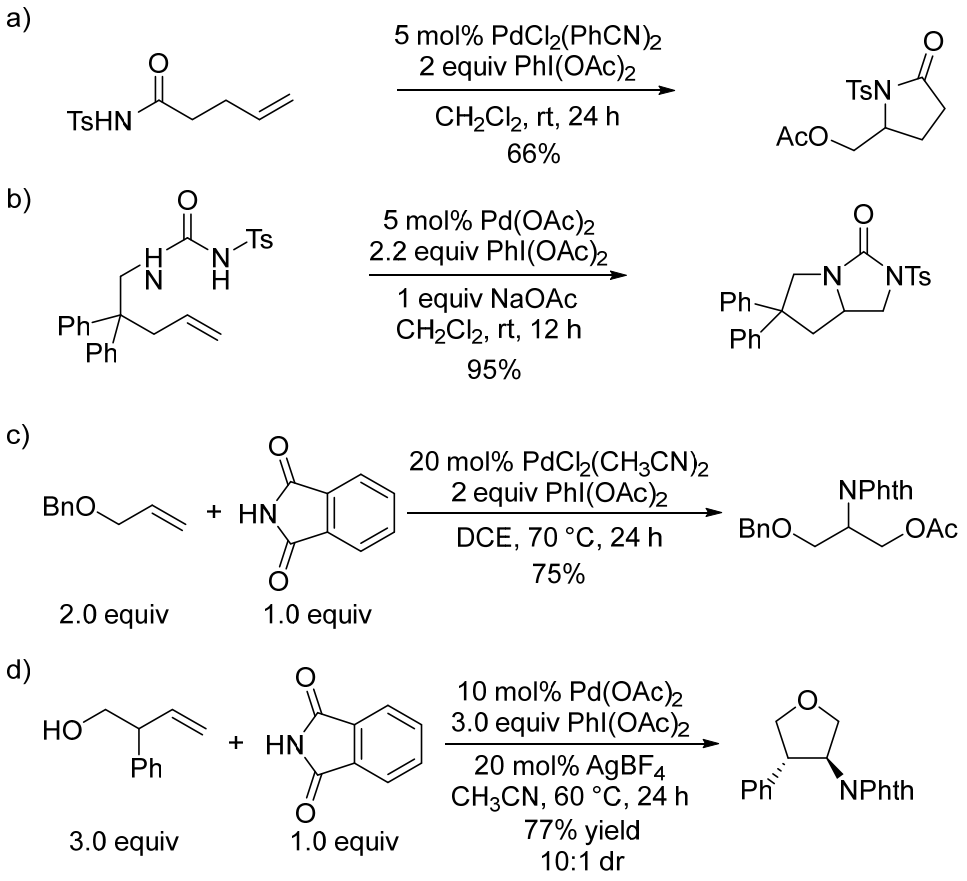


Figure 2.2. Pd(II)/Pd(IV)-catalyzed difunctionalization of olefins using $PhI(OAc)_2$ as an oxidant. a) Intramolecular aminoacetoxylation from Sorensen and co-workers, 2005. b) Intramolecular diamination from Muñiz and co-workers, 2005. c) Intermolecular aminoacetoxylation from Stahl and co-workers, 2006. d) Aminoxygenation of alkenols from Sanford and co-workers, 2007.

(Figure 2.3b).[25] In 2010, Liu and co-workers reported the use of NFSI for aminofluorination of styrenes, where NFSI acts both as a fluoride source and an amine source (Figure 2.3c).[26] Although these reactions afford difunctionalized products in high regio- and stereoselectivity, the use of excess and strong oxidants limits the functional group tolerance.

In 2009, a complementary approach was utilized by Larhed and co-workers for difunctionalization of terminal olefins, where a Pd(II)-alkyl intermediate was stabilized by

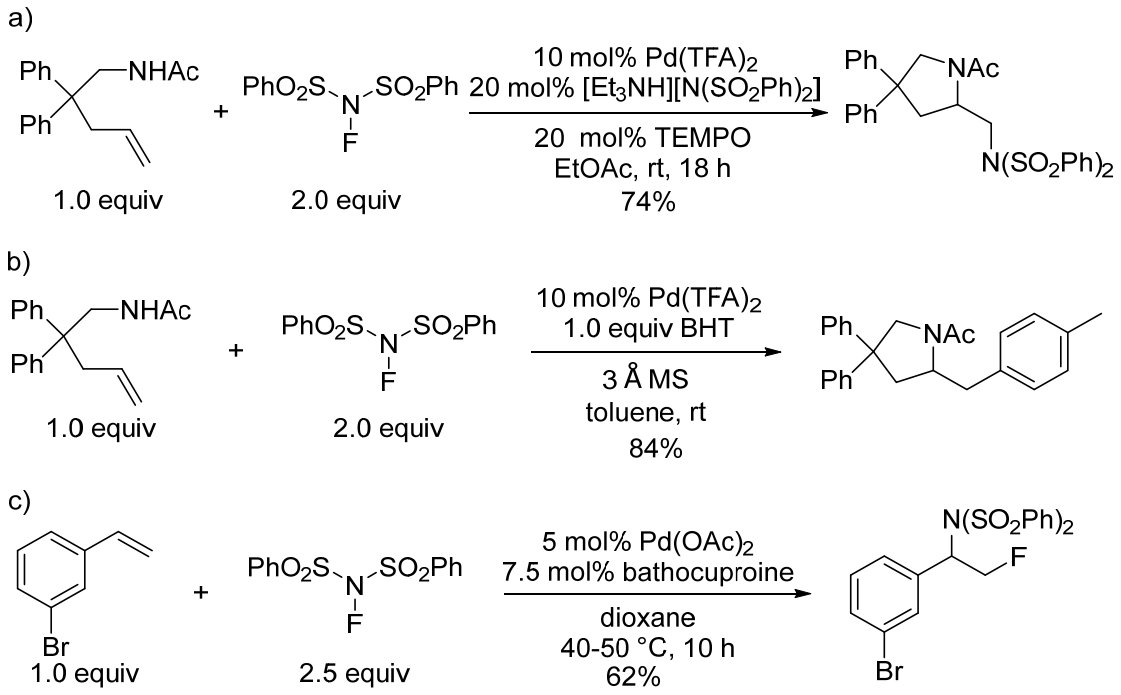


Figure 2.3. Pd(II)/Pd(IV)-catalyzed difunctionalization of olefins using NFSI as an oxidant. a) Diamination of olefins from Micheal and co-workers, 2005. b) Aminoarylation of olefins from Micheal and co-workers, 2009. c) Aminofluorination of styrenes from Liu and co-workers, 2010.

a coordinating group present within the alkene substrate (Figure 2.4).[15] For example, the diarylation of an alkene substituted with a dimethylamine group (**1**) was achieved using 5 mol% of $Pd(TFA)_2$ in the presence of phenyl boronic acid (**2**) as a coupling partner and benzoquinone (BQ) as an oxidant. Mechanistically, the first step involves transmetallation, which transfers the phenyl group from a boronic acid **2** to a Pd(II) catalyst to form Pd(II)-phenyl intermediate **A**. This is followed by alkene coordination and migratory insertion to the Pd-phenyl species **A**. Subsequent proposed chelation with the amine group stabilizes the Pd(II)-alkyl intermediate **B**, which then undergoes a transmetallation pathway with another equivalent of phenyl boronic acid (**2**), followed by reductive elimination to afford 1,2-diarylation product **3** in 81% yield and Pd(0). The Pd(0) species is oxidized by

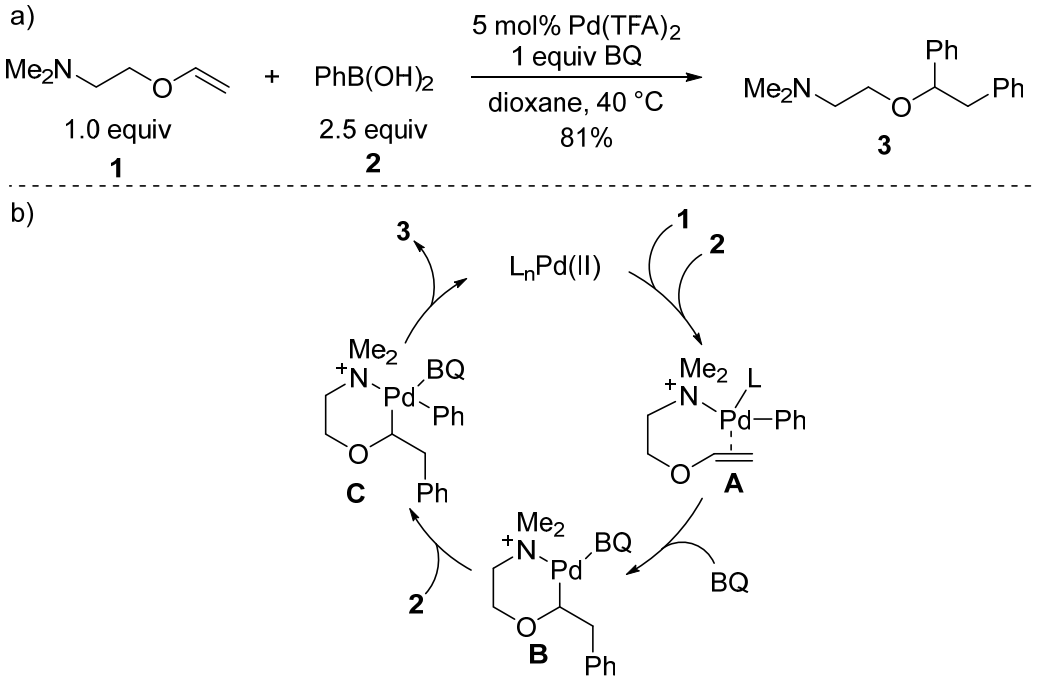


Figure 2.4. Pd(II)-catalyzed difunctionalization of olefins using chelation assisted Pd(II)-alkyl stabilization. a) General reaction. b) Proposed mechanism.

stoichiometric BQ to Pd(II), which re-enters the catalytic cycle. One major drawback of this reaction is pre-installation of a suitable group on the alkene for intramolecular chelation. Also, installation of two similar groups across the alkene makes this approach synthetically less attractive.

As discussed in Chapter 1, the Sigman group has pursued a π-allyl/benzyl formation approach for the various difunctionalization reactions of olefins. Using this approach, in 2010, they reported a Pd(II)-catalyzed 1,1-difunctionalization of terminal olefins under oxidative conditions (Figure 2.5).[27] For example, the reaction of a terminal alkene **4** with 3.0 equiv of an aryl stannane **5** gave 1,1-diarylation product **6** in 73% yield. Mechanistically, the first step involved the transmetallation of an aryl stannane **5** with Pd(II)-catalyst to form a Pd-aryl intermediate **A**. Migratory insertion of an alkene **4** is

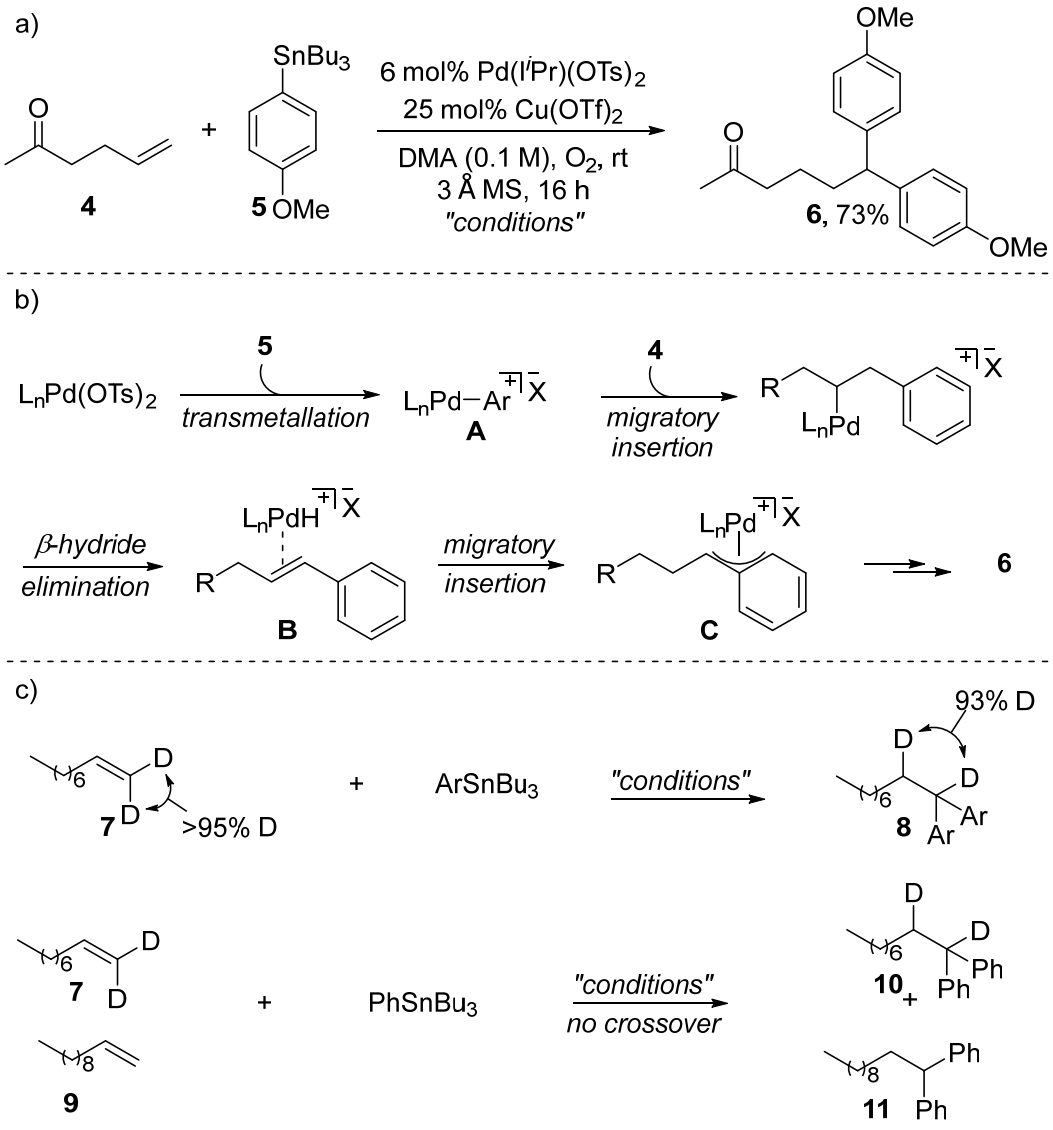


Figure 2.5. Pd(II)-catalyzed 1,1-difunctionalization of terminal alkenes. a) General reaction. b) Mechanistic hypothesis. c) Mechanistic studies.

followed by β-hydride elimination to form a Pd–H bound styrene intermediate **B**. Reinsertion into the alkene leads to the formation of a π-benzylpalladium intermediate **C**. Lastly, transmetallation with a second equivalent of coupling partner **5**, and then reductive elimination affords the 1,1-diarylation product **6**. The mechanism of the reaction has been supported by a deuterium labelling study and a cross-over experiment.[28] For example, the use of 95% deuterium incorporated alkene **7** under the reaction conditions leads to deuterium migration in the product **8**. Also, no cross-over was observed when two different terminal alkenes (**7** and **9**) were subjected to the reaction conditions ruling out Pd–H dissociation from the alkene. Although this methodology delivers the biologically relevant 1,1-diaryl motifs, the use of excess aryl stannanes, oxidative conditions, high additive loading such as 25 mol% $Cu(OTf)_2$, and installation of similar aryl groups limits the synthetic utility of this reaction.

In 2011, Sigman and co-workers reported a three-component one-pot approach, which leads to the installation of two different groups across the double bond of a terminal alkene (Figure 2.6).[29] This multicomponent reaction involves concomitant formation of two C–C bonds starting from easily accessible and/or commercially available reagents. For example, the reaction of dodecene (**12**) with cyclohexenyl triflate (**13**) and *para*-fluorophenyl boronic acid (**14**) under Pd(0) catalysis gave 77% yield of the 1,1-difunctionalized product (**15**). Mechanistically, the reaction is initiated by oxidative addition of an enol triflate **13** to Pd(0) to form a Pd-alkenyl intermediate **A**. Migratory insertion of an alkene **12** into **A** leads to the formation of an unstable Pd-alkyl adduct **B**, that rapidly undergoes β-hydride elimination, and then a second migratory insertion to form a π-allylpalladium species **C**. This presumably long lived intermediate undergoes base-

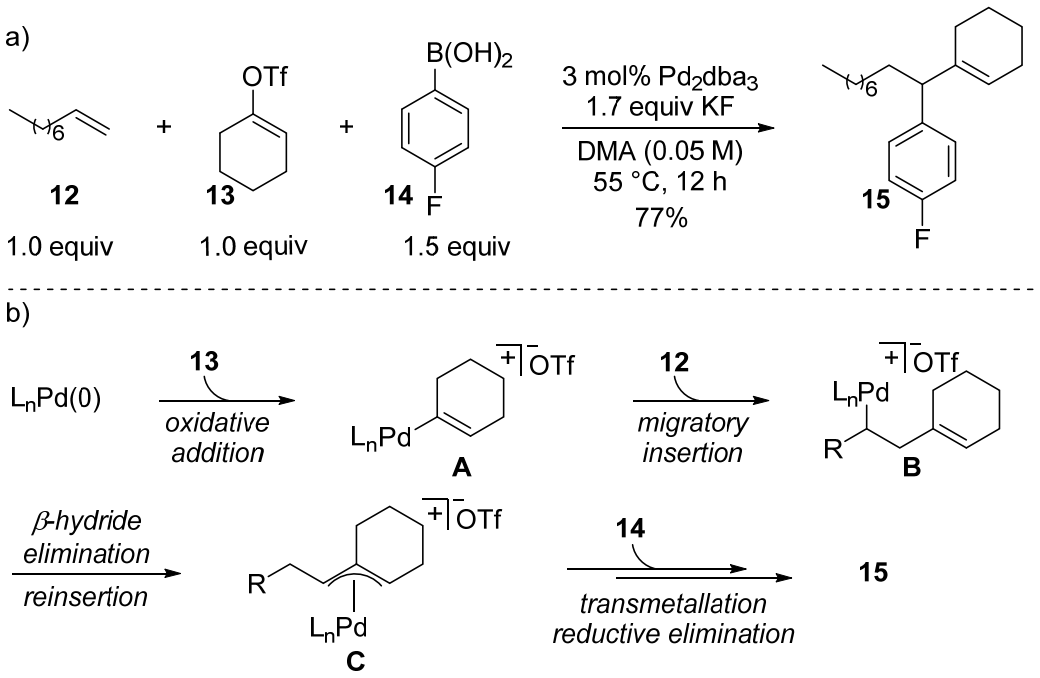


Figure 2.6. Pd(II)-catalyzed 1,1-difunctionalization of terminal alkenes. a) General reaction. b) Proposed mechanism.

assisted transmetallation with an aryl boronic acid (**14**), followed by reductive elimination to form the three component product (**15**) along with the regeneration of Pd(0) catalyst.

In conclusion, there are several ways by which a Pd(II)-alkyl species could be stabilized and further exploited to provide a platform to difunctionalize different alkenes. Though, these reactions are mechanistically intriguing, they suffer from one or more drawbacks. Our group has mainly been interested in developing Pd-catalyzed hydro- and difunctionalization reactions of olefins including terminal alkenes, styrenes etc., by trapping of the π-allyl/benzylpalladium intermediates. Although some of the previous protocols required nonoptimal conditions, recent reports have shown that the difunctionalization reactions of olefins can be achieved under mild conditions leading to a broad range of functional group tolerance.

Results and Discussion

As discussed above, our group has previously reported a Pd(0)-catalyzed 1,1-vinylarylation of terminal olefins with enol triflates and aryl boronic acids via trapping of the π-allylpalladium intermediates.[29] Inspired by this, we envisioned 1,1-vinylarylation of feedstock olefins such as ethylene, using enol triflates and aryl boronic acids in complexity generating reactions (Figure 2.7).[30] Mechanistically, the first step involves the oxidative addition of an enol triflate **16** to a Pd(0) catalyst to form a Pd(II)-alkenyl adduct **A**. It should be noted that enol triflates have been intentionally selected as a substrate because after the initial oxidative addition, the non-coordinating counterion renders the Pd-adduct **A** electrophilic, which should readily undergo ethylene coordination and migratory insertion to form Pd(II)-alkyl intermediate **B**. This intermediate can undergo β-hydride elimination and then reinsertion into the diene to form π-allylpalladium species **D**. Base-assisted transmetallation is followed by a reductive elimination pathway to form a vinylarylated product **18**. Of note, the reductive elimination can occur on either side of the π-allyl intermediate to form regioisomeric products. Nevertheless, the regioselectivity is biased by the use of six membered enol triflates, which would favor the thermodynamically more stable product with an endocyclic double bond. Also, the formation of other side products in this three-component tandem protocol cannot be ruled out. For example, the direct reaction of an enol triflate **16** with an aryl boronic acid **17** could lead to the formation of the undesired Suzuki cross-coupled product. However, it is hypothesized that the cationic character imparted by the use of a non-coordinating counterion will facilitate ethylene coordination rather than transmetallation. Also, after the first β-hydride elimination, the Pd–H can dissociate from the diene to form the undesired Heck product.

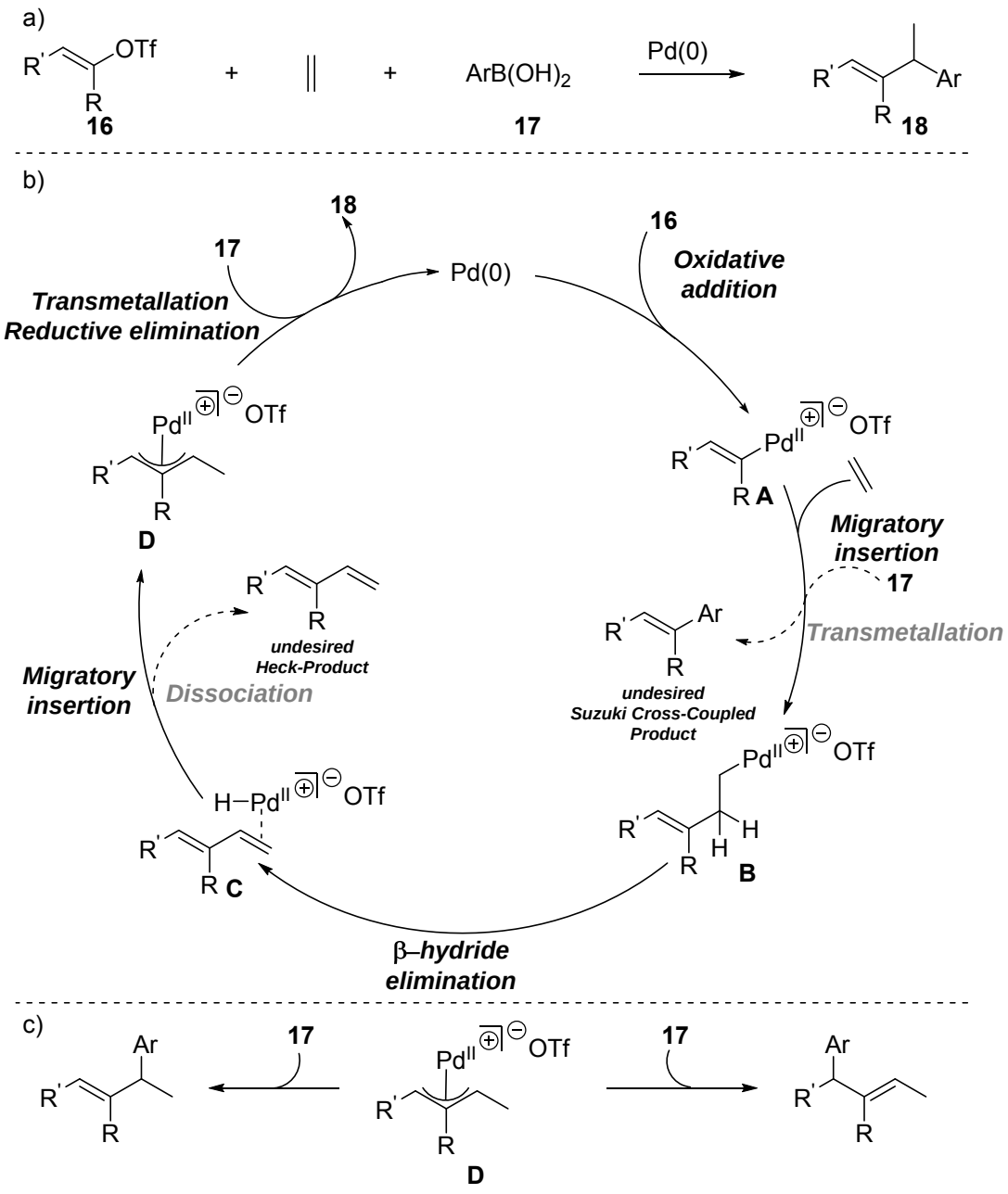
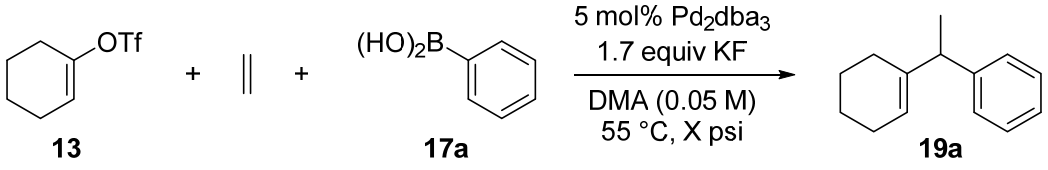


Figure 2.7. Mechanism and challenges associated with the palladium-catalyzed difunctionalization reaction of ethylene. a) General reaction. b) Proposed mechanism. c) Proposed pathway leading to two different regioisomers.

However, again, presumably the electrophilic nature of the Pd will facilitate diene coordination rather than dissociation. Additionally, there are certain challenges associated with the use of ethylene in this multicomponent approach. For example, the use of ethylene under atmospheric pressure makes it an excess reagent, which could undergo many side reactions such as palladium-mediated polymerization[31] and/or as a ligand on palladium, thus deactivating the catalyst or altering its reactivity.

With these considerations in mind, firstly the difunctionalization of ethylene at atmospheric pressure was tested, using cyclohexenyl triflate (**13**) and phenyl boronic acid (**17a**) under the conditions previously developed by our group for the vinylarylation of simple terminal olefins (Table 2.1).[29] However, only 30% yield of the desired three-component coupling product (**19a**) was observed along with the unreacted enol triflate (entry 1). Palladium black was also observed at the end of the reaction suggesting catalyst decomposition after only a few turnovers. Then the effect of ethylene pressure on the reactivity of the reaction was studied. It was observed that the increase in the pressure of ethylene from 15 psi to 30 psi did not drastically impact the yield of **19a** (entry 2). However, a further increase in pressure to 50 psi led to lower yield, presumably due to

Table 2.1. Initial optimization



13 **17a** **19a**

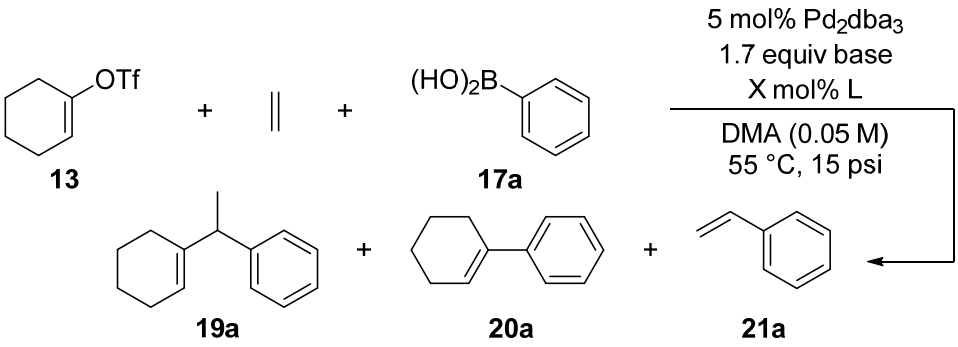
Entry	X	%conv (**13**)[a]	%yield (**19a**)[a]
1	15	37	30
2	30	30	25
3	50	25	18

[a]Determined by NMR using an internal standard.

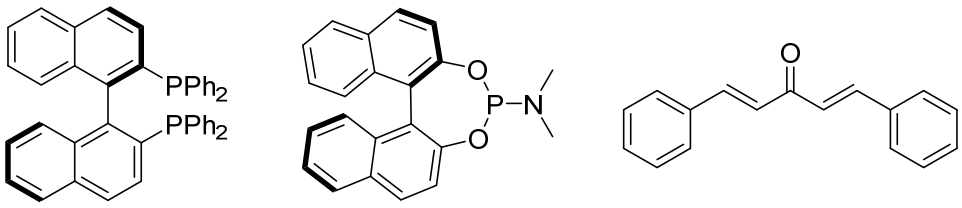
catalyst deactivation by excess ethylene (entry 3). We then turned our attention towards screening of different phosphine ligands because of their commercial availability and highly modular nature (Table 2.2). Not surprisingly, the use of monodentate electron-rich phosphine ligands gave predominantly Suzuki cross-coupled product **20a** (entries 1-4).[32] It can be hypothesized that the electron-rich character of phosphines renders the Pd(II) species less electrophilic, which would prefer transmetallation with a boronic acid rather than alkene coordination. The use of a bidentate phosphine ligand such as (*R*)-BINAP afforded mainly Heck product (**21a**). This suggests saturation of the coordination sphere of palladium after the first β-hydride elimination, which prevents coordination and reinsertion of Pd–H into the diene (entry 5).[33,34] However, the use of a hemilabile monodentate phosphine ligand such as (*R*)-monophos gave 70% yield of the product albeit as a racemate (entry 6). Also, the use of exogenous dba gave results similar to that of (*R*)-monophos (entry 7). It is possible that both these ligands stabilize Pd(0) after completion of each catalytic cycle without perturbing the electrophilicity of palladium. In fact, recently, Toste and co-workers have described the role of dba derivatives as Pd(0)-stabilizers in the arylborylation of terminal alkenes.[35] Also, the role of dba as a ligand has been described for various palladium-mediated reactions.[36] Further optimization of the reaction involving changing the base to $NaHCO_3$ (entry 8) and increasing the concentration to 0.1 M in enol triflate (entry 11), gave the desired product in 90% isolated yield. Control experiments involving removal of either dba (entry 9) or the base (entry 10) resulted in significantly lower yields.

After the optimized conditions were in hand, the scope of the reaction was explored (Figure 2.8). The use of cyclohexenyl nonaflate as an electrophile instead of cyclohexenyl

Table 2.2. Final optimization



entry	L (X mol%)	base	%yield (**19a**)[a]	ratio (**19a:20a:21a**)[a]
1	PPh_3 (20)	K_2CO_3	57	60:40:0
2	$P(^tBu)_3$ (20)	K_2CO_3	0	**20a** only
3	$P(Cy)_3$ (20)	K_2CO_3	19	30:70:0
4	Me_2PPh (20)	K_2CO_3	10	20:60:20
5	(*R*)-BINAP (10)	K_2CO_3	0	0:20:80
6	(*R*)-Monophos (10)	K_2CO_3	70	90:5:5
7	dba (15)	K_2CO_3	70	**19a** only
8	dba (15)	$NaHCO_3$	82	**19a** only
9	-	$NaHCO_3$	50	**19a** only
10	dba (15)	-	40	**19a** only
11[b]	dba (15)	$NaHCO_3$	90	**19a** only



(*R*)-BINAP (*R*)-Monophos dba

a) Determined by NMR using 2-methoxynapthalene as an internal standard.
b) The reaction was performed in 0.1 M in **13**.

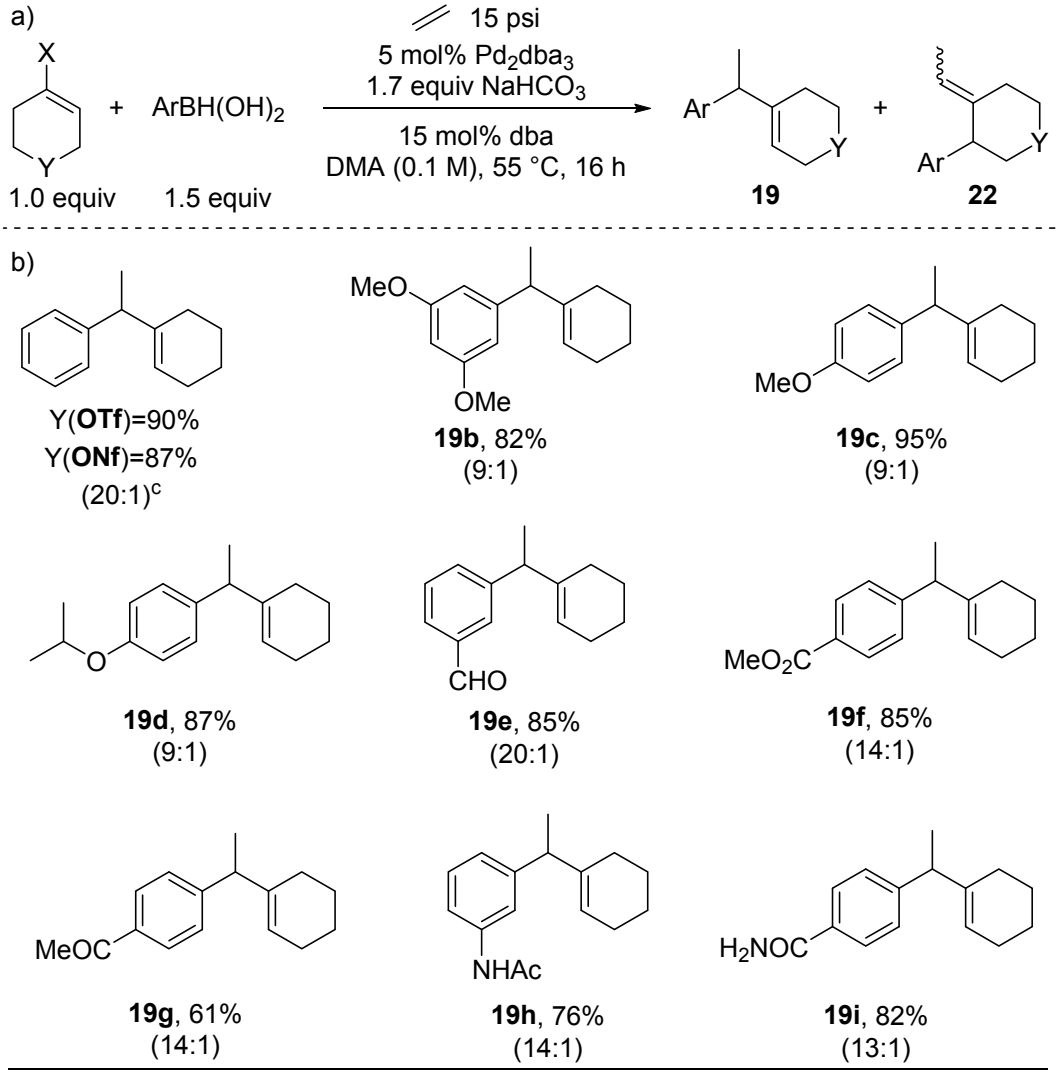


Figure 2.8. Three-component reaction of ethylene with vinyl electrophiles and aryl boronic acids. a) General reaction. b) Scope of the reaction. c) The bracket represents the regioselectivities of **19**:**22**. d) Boronic acid pinacol ester was used. *Note:* vinyl triflates and nonaflates were used interchangeably throughout (see Experimental section for synthesis of compounds **19a-19r**).

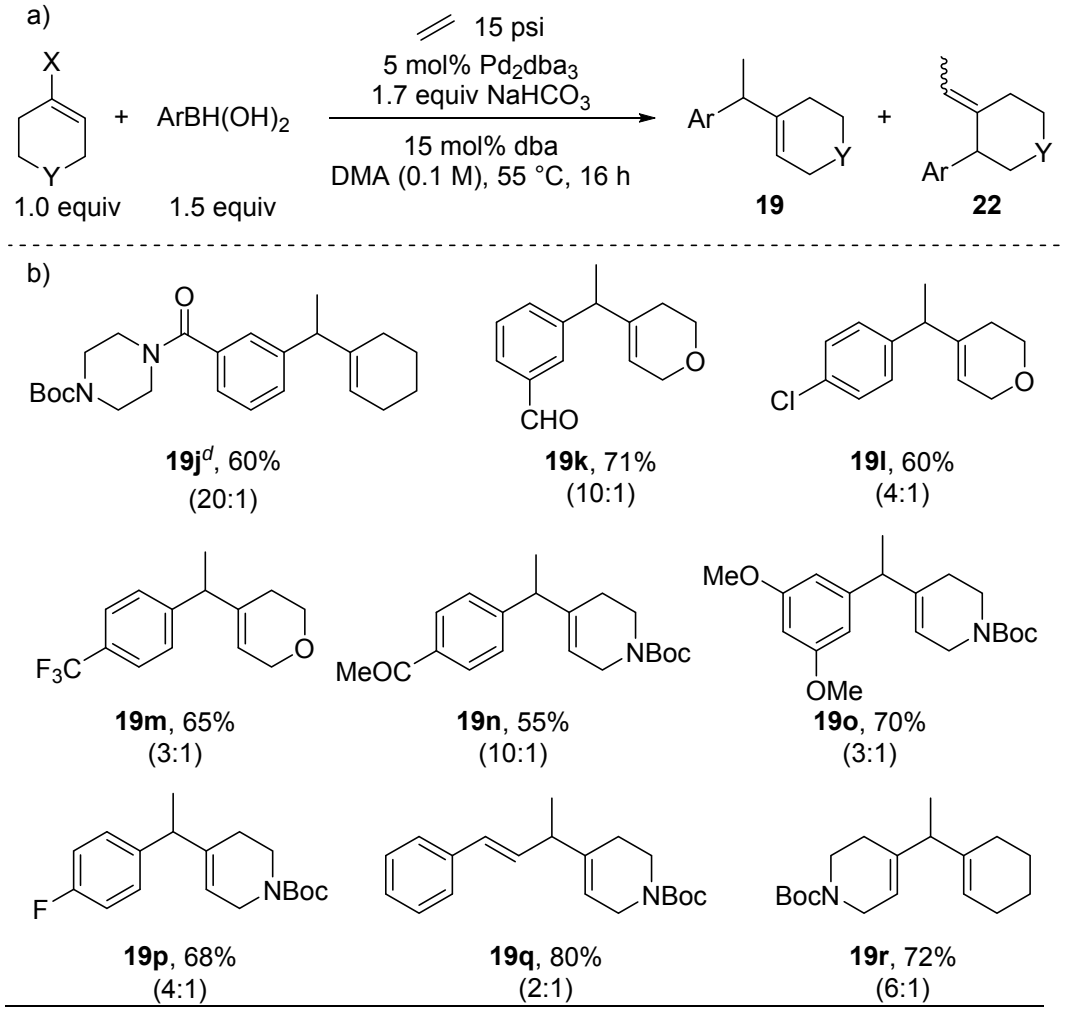


Figure 2.8. Continued.

triflate gave comparable results. It should be noted that, although, vinyl triflates are more efficient in terms of atom-economy, they are relatively less stable and cost-effective compared to their nonaflate counterpart.[37] Vinyl triflates and nonaflates were used interchangeably in the reaction. In addition to phenyl boronic acid, other electronically varied aryl boronic acids provided the desired difunctionalized products in good yields and regioselectivities. For example, aryl boronic acid with electron-rich groups at the *para*-position, such as methoxy (**19b**) and isopropoxy (**19c**), gave excellent yields and high regioselectivities. Also, aryl boronic acids with various functional groups such as an aldehyde (**19e**, **19k**), an ester (**19f**), a ketone (**19g**, **19n**), a free amide (**19i**), a secondary amide (**19h**) and a tertiary amide (**19j**) were well tolerated. Halogen substituted boronic acids such as 4-chloro-, 4-trifluoromethyl-, and 4-fluoro phenyl boronic acid (**19l, 19m, 19p**) afforded the corresponding products in good yields. Various six membered vinyl electrophiles containing oxygen and Boc-protected nitrogen groups afforded products in good yields and modest regioselectivity (**19k**-**19q**). In addition, the use of (*E*)-*β*-styryl (**19q**) and (*E*)-alkenyl boronic acid (**19r**) gave the product in high yields but low regioselectivities. The reason for the low regioselectivity is unknown at this stage. In general, since the regioselectivity for the formation of 1,1-vinylarylation product is substrate controlled, the scope of the electrophiles is limited to six membered rings.

Since, heteroaromatic groups are found in a wide variety of natural products and biologically active molecules, we envisioned a three-component reaction of ethylene and vinyl triflates with heteroaromatic cross-coupling partners. However, transition-metal-catalyzed coupling of these organometallic reagents is challenging, particularly because of their ability to undergo rapid protodeborylation.[38,39] Additionally, Lewis basicity and slow

rate of transmetallation limit their successful use in the coupling reactions.[40,41] Not surprisingly, the use of 4-pyridyl boronic acid (**24a**) under the reaction conditions led to less than 10% yield of the three-component product (**25a**) with recovery of the rest of the vinyl triflate (Figure 2.9). However, switching from a boronic acid to a boronic ester led to an excellent yield of the desired product with only a single regioisomer observed. With modest optimization, such as an increase in the reaction time and temperature, different heteroaromatic boronic esters were explored (Figure 2.10). For example, the use of five membered heterocycles such as pyrazoles (**25b**, **25c**) and an isoxazole (**25d**) gave the corresponding products in synthetically useful yields. In addition, the more challenging substrates such as 3-quinoline (**25e**) and 2-chloro 4-pyridyl (**25f**) boronic esters gave excellent yields of the desired products. The use of 2-pyridyl boronic ester predominantly underwent protodeborylation.[42,43] However, replacement of the Bpin derivative with the corresponding Stille reagent led to an excellent yield of the three-component coupling product (**25g**). Finally, the scope of the reaction in terms of the olefin partner can be extended to a simple terminal alkene. As shown in Figure 2.11, the use of dodecene under the reaction conditions gave the desired three-component product (**26**) in 65% yield.

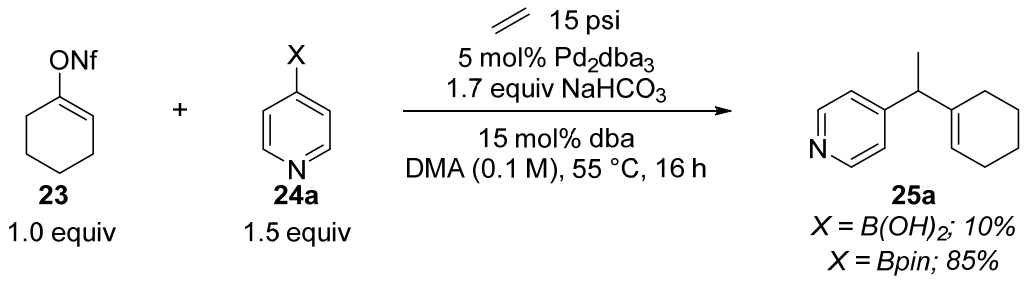


Figure 2.9. Three-component cross-coupling reaction of ethylene with 4-pyridyl boronic acid and ester.

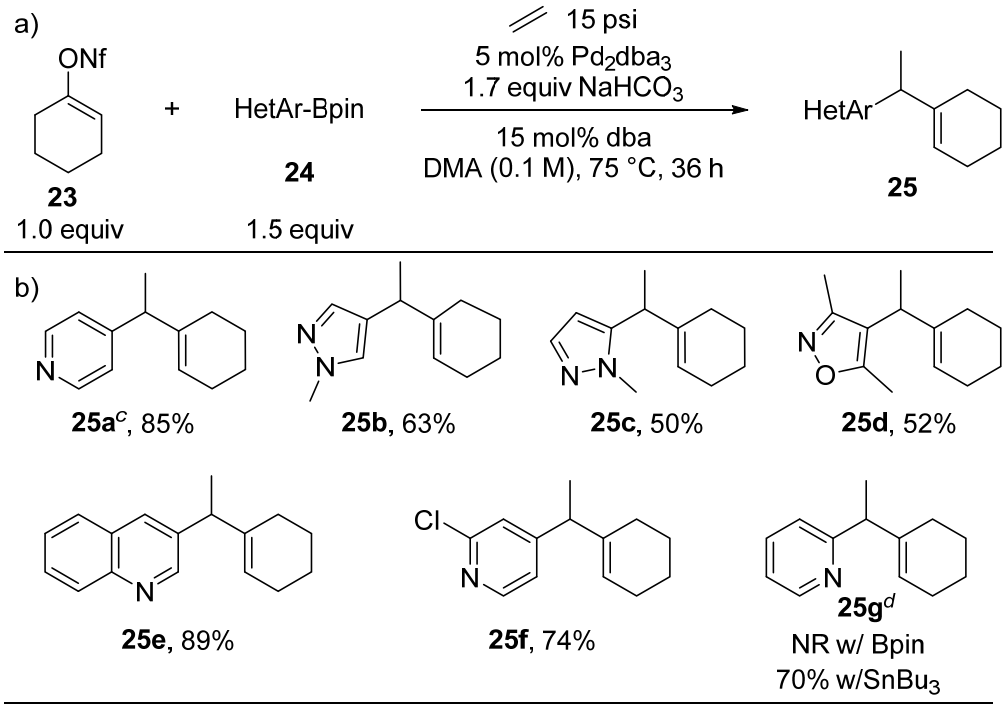


Figure 2.10. Three-component reaction of ethylene with cyclohexenyl nonaflate and heteroaromatic boronic esters. a) General reaction. b) Scope of the reaction. c) Reaction performed at 55 °C for 16 h. d) Reaction performed at 55 °C using CsF as base.

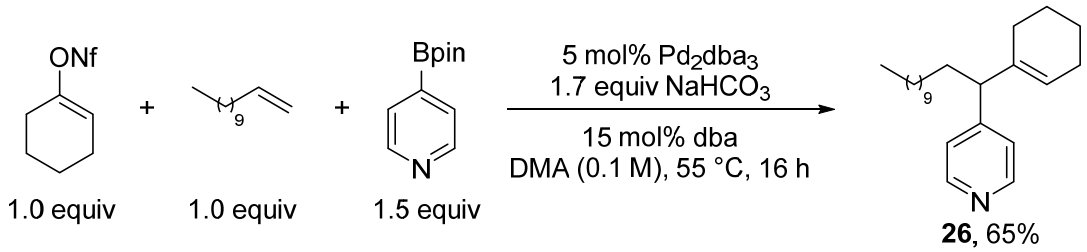


Figure 2.11. Three-component cross-coupling reaction of dodecene with cyclohexenyl nonaflate and 4-pyridyl boronic ester.

Negative Results

The reaction of *ortho*-substituted aryl boronic acids such as 2-methylphenyl boronic acid, has been found to be troublesome, as low yield (< 30%) as well as low regioselectivity (**A:B** = 1.4) was observed (Figure 2.12a). Although, the use of a seven membered vinyl triflate afforded good yield of the three-component products **C** and **D**, a 1:1 mixture of regioisomers was obtained (Figure 2.12b). The vinyl triflate derived from trimedone (**E**) and cyclic six-membered lactone (**F**) were not tolerated under the reaction conditions (Figure 2.12c). The use of cyclohexenyl tosylate (**G**) as an electrophile led to complete recovery of the starting material and no reaction was observed; probably because of the slow oxidative addition of the vinyl tosylate. The efficiency of the three-component reaction of ethylene with heteroaromatic cross-coupling partners is highly dependent on the electronic nature of nucleophile (Figure 2.12d). For example, the reaction with 3-pyridyl boronic ester (**H**) and 2-(tributylstannyl)furan (**I**) failed to yield the desired product. Also, the use of 4-isoquinoline boronic ester (**J**) underwent protodeborylation exclusively. Thiophene 2- and 3-boronic esters (**K, L**) completely shut down the reaction and no three-component product was isolated, probably because of the deactivation of catalyst by sulphur.

Conclusion

We have developed a highly regioselective Pd-catalyzed difunctionalization of ethylene involving the addition of a vinyl group and an aryl group across one end of ethylene. The process allows formation of complex molecules starting from ethylene, and easily accessible vinyl triflates/nonaflates and boronic acids/esters. A key step in the

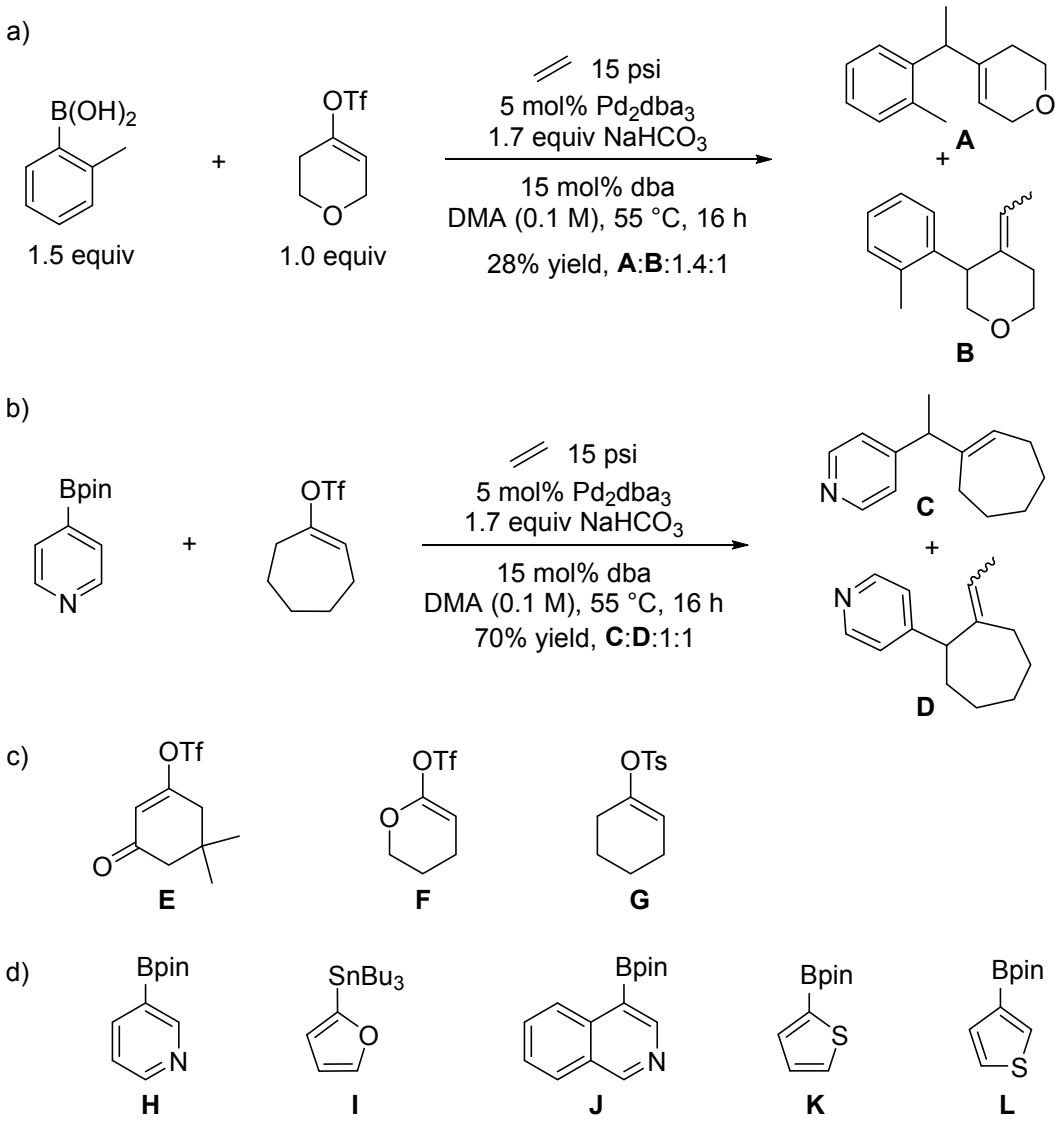


Figure 2.12. Negative results. a) Reaction with 2-methyl phenyl boronic acid. b) Reaction with seven membered vinyl triflate. c) Unsuccessful use of some vinyl electrophiles. d) Unsuccessful use of some heteroaromatic boronic esters.

optimization of the reaction conditions was the use of dba as a ligand, which drastically improved the reaction. The scope of the reaction is very broad, as a wide variety of aryl boronic acids have been tolerated under the reaction conditions. Furthermore, the reaction allows the utilization of heteroaromatic cross-coupling partners, a first in the difunctionalization reactions developed in the Sigman group.

Experimental

General considerations

Toluene, THF and CH_2Cl_2 were passed through an alumina column (innovative technology) solvent system. Dimethylacetamide (DMA) was purchased from Sigma-Aldrich (anhydrous, 99.8%, water < 0.005%) and dried over 3Å molecular sieves (activated by heating with a Bunsen burner while under vacuum). Ethylene was used as purchased from Sigma-Aldrich (≥ 99.5 % purity). All other reagents were used as purchased unless mentioned otherwise. Vinyl triflates and nonaflates were synthesized according to previous procedures.[44-46] Tris(dibenzylideneacetone)dipalladium(0) was prepared according to a published procedure.[47] Boronic acids pinacol esters (Bpin) were used as purchased or synthesized from boronic acids by a standard procedure.[48] The thick-walled Schlenk bombs used in the reaction were washed with aqua regia and then repeatedly with water and finally with acetone and dried in an oven for 12 h before use. ^{1}H NMR spectra were obtained at 300 MHz, 400 MHz or 500 MHz, chemical shifts are reported in ppm, and referenced to the $CHCl_3$ singlet at 7.26 ppm. The chemical shifts of proton resonances are reported using the following format: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet), coupling constant(s) (*J*

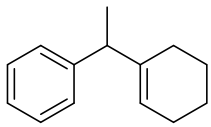
in Hz), integral]. ^{13}C NMR spectra were obtained at 75 MHz, 100 MHz or 126 MHz and referenced to the center line of the $CDCl_3$ triplet at 77.23 ppm. Flash chromatography was performed using EM reagent silica 60 (230-400 mesh). IR spectra were recorded using a Thermo Nicolet FT-IR. High resolution mass spectrometry (HRMS) data were obtained on a Waters LCP Premier XE instrument by ESI/TOF. Achiral GC (gas chromatography) was performed using a Hewlett Packard HP 6890 series GC system fitted with an Agilent HP-5 column. *Note:* The ^{1}H NMR and ^{13}C NMR spectra of unknown compounds can be obtained through Marriot Library.

General procedure for optimization

The general procedure A, described below, was used with the modifications described in Tables 2.1 and 2.2. The reaction was performed on 0.10 mmol scale with ~ 10 wt% 2-methoxynapthalene used as an internal standard. After the required reaction time, the reaction mixture was passed through a small celite pipet with ethyl acetate and analyzed by ^{1}H NMR for product formation.

General procedure A for the 1,1 vinylarylation of ethylene

1-(1-(cyclohex-1-en-1-yl) ethyl)-4-methoxybenzene (**19a**):



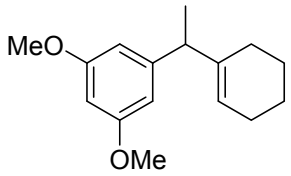
19a

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 91 mg of phenyl boronic

acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 115 mg of cyclohexenyl triflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The Schlenk bomb was then evacuated followed by pressurization with ethylene at 15 psi at room temperature. This process was repeated three times and the bomb was sealed with teflon stopcock. All the reagents were weighed outside the glove box. The reaction mixture was stirred during the process of evacuation and pressurization. The reaction mixture was heated to 55 °C in an oil bath and stirred vigorously for 16 h. After this time, the reaction mixture was cooled to room temperature and then filtered through celite with ether (50 mL). The solution was diluted with additional ether (100 mL) and transferred to a separatory funnel and washed with H_2O (3x30 mL) followed by brine (1x10 mL). The organic layer was then dried over anhydrous sodium sulfate. After filtration, the solvents were removed via rotary evaporation. At this stage, ^{1}H NMR of crude reaction mixture was taken to determine the ratio of the regioisomers by comparing the peaks of vinylic hydrogens of both the isomers. The product was purified by silica gel flash chromatography by eluting with 100% hexanes to give the product as a colorless oil in 90% yield (84 mg, 0.45 mmol), inseparable mixture of regioisomers (**19a:22a::20:1**), R_f = 0.5 (100% hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (t, *J* = 8.0 Hz, 2H), 7.24-7.18 (m, 3H), 5.64-5.58 (m, 1H), 4.68 (q, *J* = 7.0 Hz, 1H) minor, 3.31 (q, *J* = 7.5 Hz, 1H), 2.13-2.05 (m, 2H), 1.84-1.73 (m, 2H), 1.59-1.53 (m, 4H), 1.36 (d, *J* = 7.0 Hz, 3H). Additional peaks at δ 1.28 (bs) and 0.90 (m) are observed due to polyethylene; ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.2, 141.4, 128.9 (minor), 128.3, 128.3 (minor), 127.7, 126.0, 120.9, 117.1 (minor), 50.9 (minor), 46.7, 34.0 (minor), 28.5 (minor), 27.9 (minor), 27.4, 26.3 (minor), 25.6, 23.3, 22.9, 20.0; IR (neat): 2965 (s), 2925 (s), 2856 (m), 1600 (w), 1491 (m), 1450 (m), 1024 (m), 918 (w), 843 (m), 763 (w), 699 (s) cm^{-1}.

Additional peak at δ 29.9 is observed due to polyethylene contaminant. NMR (^{1}H, ^{13}C), IR and HRMS of this compound have been reported.[3]

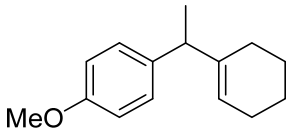
1-(1-(cyclohex-1-en-1-yl)ethyl)-3,5-dimethoxybenzene (**19b**):



19b

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 136 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 115 mg of cyclohexenyl triflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19b**. The product was purified by silica gel flash chromatography by eluting with 1.5% EtOAc in hexanes to give product as colorless oil in 82% yield (101 mg, 0.41 mmol), inseparable mixture of regioisomers (**19b:22b::9:1**), R_f = 0.3 (5% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38 (d, J = 2.4 Hz, 2H), 6.30 (t, J = 2.0 Hz, 1H), 5.63-5.57 (m, 1H), 4.78 (q, J = 7.0 Hz, 1H) minor, 3.78 (s, 6H), 3.22 (q, J = 7.0 Hz, 1H), 2.10-2.02 (m, 2H), 1.90-1.70 (m, 2H), 1.60-1.50 (m, 4H), 1.32 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 148.9, 146.6, 141.1, 121.0, 117.2, 107.0, 106.0, 98.0, 55.4, 51.1, 47.0, 34.0, 28.4, 27.9, 27.4, 26.2, 25.6, 23.3, 22.8, 19.9; IR (neat): 2926 (s), 2855 (w), 2834 (m) 1592 (s), 1456 (s), 1340 (m), 1202 (s), 1067 (m), 1030 (m), 919 (w), 829 (m), 700 (m), 668 (m) cm^{-1}; HRMS (ESI+) calculated for $C_{16}H_{22}O_2$ *m/z* (M+H) 247.1698, obsd. 247.1698.

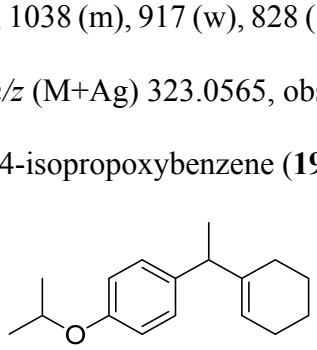
1-(1-(cyclohex-1-en-1-yl)ethyl)-4-methoxybenzene (**19c**):



19c

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 114 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 116 mg of cyclohexenyl triflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19c**. The product was purified by silica gel flash chromatography by eluting with 1.5% EtOAc in hexanes to give product as colorless oil in 95% yield (103 mg, 0.48 mmol), inseparable mixture of regioisomers (**19c:22c::9:1**), R_f = 0.3 (5% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.61-5.56 (m, 1H), 4.69 (q, *J* = 7.0 Hz, 1H) minor, 3.80 (s, 3H), 3.30 (q, *J* = 7.0 Hz, 1H), 2.13-2.02 (m, 2H), 1.84-1.73 (m, 2H), 1.58-1.53 (m, 4H), 1.33 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0, 141.8, 138.3, 128.6, 120.6, 113.7, 55.4, 45.9, 27.3, 25.6, 23.3, 22.9, 20.1; IR (neat): 2925 (s), 2854 (w), 2833 (m) 1610 (m), 1509 (s), 1456 (m), 1300 (w), 1242 (s), 1038 (m), 917 (w), 828 (s), 763 (w), 668 (m) cm^{-1}; HRMS (ESI+) calculated for $C_{15}H_{20}O$ *m/z* (M+Ag) 323.0565, obsvd. 323.0569

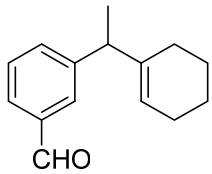
1-(1-(cyclohex-1-en-1-yl)ethyl)-4-isopropoxybenzene (**19d**).



19d

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 135 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 115 mg of cyclohexenyl triflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19d**. The product was purified by silica gel flash chromatography by eluting with 1% EtOAc in hexanes to give product as colorless oil in 87% yield (106 mg, 0.43 mmol), inseparable mixture of regioisomers (**19d:22d::9:1**), R_f = 0.6 (5% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.61-5.56 (m, 1H), 4.54 (septet, J = 6.3 Hz, 1H), 3.27 (q, J = 7.2 Hz, 1H), 2.13-2.02 (m, 2H), 1.92-1.73 (m, 2H), 1.60-1.54 (m, 4H), 1.39-1.34 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 141.7, 138.0, 128.5, 120.5, 115.6, 69.9, 45.9, 27.2, 25.5, 23.3, 22.9, 22.3, 20.0; IR (neat): 2973 (s), 2927 (s), 1609 (m), 1506 (w), 1450 (m), 1382 (m), 1297 (w), 1237 (s), 1181 (m), 1119 (s), 1013 (m), 955 (s), 829 (s), 667 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{17}H_{24}O$ *m/z* (M+H) 245.1905, obsd. 245.1908.

3-(1-(cyclohex-1-en-1-yl)ethyl)benzaldehyde (**19e**).

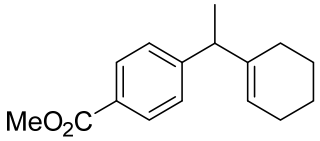


19e

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 112 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 115 mg of cyclohexenyl triflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19e**. The product was purified by silica gel flash

chromatography by eluting with 1.5% EtOAc in hexanes to give product as colorless oil in 85% yield (91 mg, 0.42 mmol), inseparable mixture of regioisomers (**19e:22e::20:1**), R_f = 0.3 (5% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 7.70 (m, 2H), 7.45 (m, 2H), 5.63-5.60 (m, 1H), 4.61 (q, *J* = 7.0 Hz, 1H) minor, 3.38 (q, *J* = 7.2 Hz, 1H), 2.12-2.03 (m, 2H), 1.84-1.68 (m, 2H), 1.58-1.50 (m, 4H), 1.37 (d, *J* = 7.2 Hz, 3H). Peaks at δ 1.26 (bs) and 0.88 (m) are observed due to polyethylene. ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9, 147.3, 140.7, 136.7, 135.3, 134.1, 130.1, 129.1, 128.8, 127.9, 121.8, 50.5, 46.5, 28.5, 27.8, 27.3, 26.1, 25.5, 23.2, 22.7, 19.7; IR (neat): 2933 (s), 2855 (m), 1698 (s), 1601 (w), 1447 (m), 1375 (w), 1236 (m), 1188 (m), 915 (m), 800 (m), 701 (s), 668 (m) cm^{-1}. Peak at δ 29.9 is due to polyethylene. HRMS (ESI+) calculated for $C_{15}H_{18}O$ *m/z* (M+H) 215.1436, obsd. 215.1439.

Methyl 4-(1-(cyclohex-1-en-1-yl)ethyl)benzoate (**19f**):

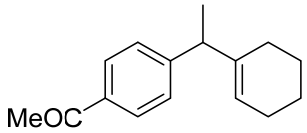


19f

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 135 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 190 mg of cyclohexenyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19f**. The product was purified by silica gel flash chromatography by eluting with 1% EtOAc in hexanes to give product as colorless oil in 85% yield (104 mg, 0.43 mmol), inseparable mixture of regioisomers (**19f:22f::14:1**), R_f = 0.5 (5% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97-

7.93 (td, *J* = 8.4, 2.0 Hz, 2H), 7.28-7.25 (m, 2H), 5.63-5.58 (m, 1H), 4.61 (q, *J* = 7.0 Hz, 1H) minor, 3.90 (s, 3H), 3.34 (q, *J* = 7.2 Hz, 1H), 2.12-2.03 (m, 2H), 1.82-1.67 (m, 2H), 1.57-1.51 (m, 4H), 1.34 (d, *J* = 7.2 Hz, 3H). Additional peaks at δ 1.26 (bs) and 0.88 (m) are observed due to polyethylene. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 151.8, 140.7, 129.8, 129.6, 128.9, 128.1, 127.7, 121.6, 52.1, 50.9, 46.8, 33.8, 28.5, 27.8, 27.4, 26.1, 25.5, 23.18, 22.7, 19.6. Peak at δ 29.9 is due to polyethylene. IR (neat): 2926 (s), 2856 (w), 2836 (w), 1720 (s), 1608 (m), 1432 (m), 1341 (m), 1274 (s), 1174 (m), 1104 (s), 1018 (m), 918 (w), 857 (m), 772 (m), 708 (m), 667 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{16}H_{20}O_2$ *m/z* (M+Na) 267.1361, obsd. 267.1361.

1-(4-(1-(cyclohex-1-en-1-yl)ethyl)phenyl)ethanone (**19g**):

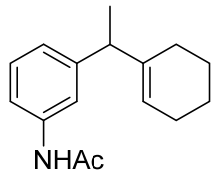


19g

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 123 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 115 mg of cyclohexenyl triflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19g**. The product was purified by silica gel flash chromatography by eluting with 2.5% EtOAc in hexanes to give product as colorless oil in 61% yield (70 mg, 0.31 mmol), inseparable mixture of regioisomers (**19g:22g::14:1**), R_f = 0.3 (5% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95-7.87 (m, 2H), 7.36-7.28 (m, 2H), 5.68-5.60 (m, 1H), 4.61 (q, *J* = 7.0 Hz, 1H) minor, 3.37 (q, *J* = 7.2 Hz, 1H), 2.62-2.59 (m, 3H), 2.14-2.04 (m, 2H), 1.84-1.67 (m, 2H), 1.60-1.52 (m, 4H), 1.37 (d, *J* = 7.2

Hz, 3H). Peaks at 1.26 (bs) and 0.88 (m) are observed due to polyethylene. ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.1, 152.1, 140.5, 135.3, 128.6, 127.9, 121.7, 117.7, 46.8, 33.8, 28.5, 27.8, 27.4, 26.8, 25.5, 23.2, 22.7, 19.6. Peak at δ 29.9 is observed due to polyethylene. IR (neat): 2925 (s), 2855 (m), 2835 (w), 1681 (s), 1604 (s), 1569 (w), 1411 (m), 1356 (m), 1265 (s), 1180 (m), 1074 (w), 1015 (w), 954 (m), 917(w), 829 (m), 687 (m), 596 (s) cm^{-1}; HRMS (ESI+) calculated for $C_{16}H_{20}O$ *m/z* (M+H) 229.1592, obsd. 229.1594.

N-(3-(1-(cyclohex-1-en-1-yl)ethyl)phenyl)acetamide (**19h**):

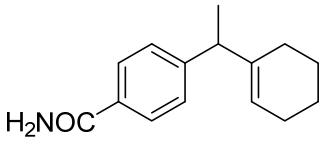


19h

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 134 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 190 mg of cyclohexenyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19h**. The product was purified by silica gel flash chromatography by eluting with 15% acetone in hexanes to give product as colorless oil in 76% yield (92 mg, 0.38 mmol), inseparable mixture of regioisomers (**19h:22h::14:1**), R_f = 0.3 (20% acetone in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (dd, *J* = 7.8, 1.0 Hz, 2H), 7.26-7.18 (m, 2H), 6.95 (d, *J* = 7.8 Hz, 1H), 5.61-5.54 (m, 1H), 4.67 (q, *J* = 6.6 Hz, 1H) minor, 3.26 (q, *J* = 7.0 Hz, 1H), 2.15 (s, 3H), 2.10-2.00 (m, 2H), 1.86-1.66 (m, 2H), 1.58-1.50 (m, 4H), 1.31 (d, *J* = 7.2 Hz, 3H). Peaks at 1.26 (bs) and 0.88 (m) are observed due to polyethylene. ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 147.2, 141.1, 138.0, 128.9, 124.8, 123.7, 121.0, 120.3, 119.1, 117.8, 117.2, 53.9, 50.7, 46.6, 40.1, 33.8, 29.5,

28.4, 27.8, 27.3, 25.5, 24.8, 23.2, 22.8, 19.8. Peak at δ 29.9 is observed due to polyethylene. IR (neat): 3310 (m), 2926 (s), 1734 (s), 1669 (s), 1609 (s), 1550 (s), 1435 (s), 1365 (s), 1321 (m), 1220 (s), 1016 (m), 918 (w), 885 (m), 791 (s), 702 (s), 667 (m) cm^{-1}; HRMS (ESI+) calculated for $C_{16}H_{21}NO$ *m/z* (M+H) 244.1701, obsd. 244.1705.

4-(1-(cyclohex-1-en-1-yl)ethyl)benzamide (**19i**):

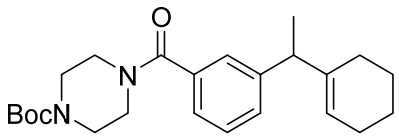


19i

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 124 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 190 mg of cyclohexenyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19i**. The product was purified by silica gel flash chromatography by eluting with 1% DCM in MeOH to give product as white solid in 82% yield (94 mg, 0.41 mmol), inseparable mixture of regioisomers (**19i:22i::13:1**), Mp = 117-120 °C, R_f = 0.1 (1% DCM in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.90 (bs, 2H), 5.64-5.58 (m, 1H), 4.62 (q, *J* = 6.4 Hz, 1H) minor, 3.34 (q, *J* = 7.0 Hz, 1H), 2.12-2.03 (m, 2H), 1.82-1.68 (m, 2H), 1.58-1.51 (m, 4H), 1.34 (d, *J* = 6.8 Hz, 3H). Peaks at 1.26 (bs) and 0.88 (m) are observed due to polyethylene. ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 150.8, 140.7, 131.2, 129.1, 128.0, 127.6, 127.4, 121.7, 46.7, 33.8, 27.4, 26.1, 25.5, 23.2, 22.8, 19.7. Peak at δ 29.9 is observed due to polyethylene. IR (neat): 3198 (m), 2925 (s), 2861 (w), 2833 (m), 1653 (s), 1613 (s),

1566 (w), 1416 (s), 1387 (m), 857 (m), 667 (s) cm^{-1}; HRMS (ESI+) calculated for $C_{15}H_{19}NO$ *m/z* (M+H) 230.1545, obsd. 230.1540.

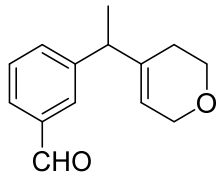
Tert-butyl 4-(3-(1-(cyclohex-1-en-1-yl)ethyl)benzoyl)piperazine-1-carboxylate (**19j**):



19j

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 312 mg of aryl boronic acid pinacol ester (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 115 mg of vinyl triflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19j**. The product was purified by silica gel flash chromatography by eluting with 15% EtOAc in hexanes to give product as colorless oil in 60% yield (120 mg, 0.30 mmol), single regioisomer, R_f = 0.2 (20% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.15 (m, 4H), 5.57-5.53 (m, 1H), 3.90-3.20 (m, 9H), 2.05-1.96 (m, 2H), 1.78-1.63 (m, 2H), 1.52-1.40 (m, 13H), 1.29 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.1, 154.8, 146.6, 140.8, 135.4, 129.3, 128.6, 126.2, 124.8, 121.5, 80.5, 47.7, 46.5, 28.5, 27.3, 25.5, 23.1, 22.7, 19.7; IR (neat):): 2971 (m), 2925 (s), 2856 (m), 1696 (s), 1638 (s), 1581 (w), 1455 (w), 1411 (s), 1364 (s), 1286 (m), 1244 (s), 1164 (s), 1116 (s), 1014 (s), 996 (m), 918 (m), 864 (w), 804 (w), 710 (w), 668 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{24}H_{34}N_2O_3$ *m/z* (M+Na) 421.2467, obsd. 421.2471.

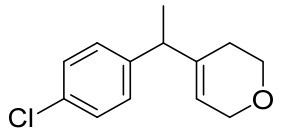
3-(1-(3,6-dihydro-2H-pyran-4-yl)ethyl)benzaldehyde (**19k**):



19k

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 113 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 191 mg of vinyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19k**. The product was purified by silica gel flash chromatography by eluting with 8% EtOAc in hexanes to give product (only **19k**) as colorless oil in 71% yield (77 mg, 0.36 mmol), separable regioisomers (**19k:22k::10:1**), R_f = 0.2 (10% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 7.76-7.70 (m, 2H), 7.50-7.45 (m, 2H), 5.65-5.59 (m, 1H), 4.23-4.18 (m, 2H), 3.76-3.67 (m, 2H), 3.44 (q, *J* = 7.0 Hz, 1H), 1.94-1.86 (m, 2H), 1.40 (d, *J* = 7.2 Hz, 3H). Peaks at 1.26 (bs) and 0.88 (m) are observed due to polyethylene. ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.7, 146.1, 138.7, 136.9, 134.0, 129.3, 128.6, 128.4, 120.6, 65.8, 64.5, 45.8, 27.5, 19.4. Peaks at δ 29.9 and 30.5 are observed due to polyethylene. IR (neat): 2969 (s), 2931 (m), 1697 (s), 1600 (w), 1584 (w), 1445 (m), 1365 (m), 1221 (s), 1129 (s), 934 (s), 800 (m), 698 (s), 649 (m) cm^{-1}. HRMS (ESI+) calculated for $C_{14}H_{16}O_2$ *m/z* (M+H) 217.1229, obsd. 217.1224.

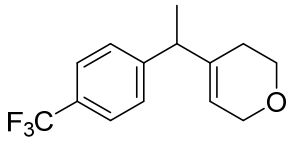
4-(1-(4-chlorophenyl)ethyl)-3,6-dihydro-2H-pyran (**19l**):



19l

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 117 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 191 mg of vinyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19l**. The product was purified by silica gel flash chromatography by eluting with 2.5% EtOAc in hexanes to give product as colorless oil in 60% yield (67 mg, 0.30 mmol), separable regioisomers (**19l:22l::4:1)**, R_f = 0.3 (5% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.24 (m, 2H), 7.14-7.11 (m, 2H), 5.59-5.55 (m, 1H), 4.21-4.17 (m, 2H), 3.75-3.66 (m, 2H), 3.32 (q, *J* = 7.0 Hz, 1H), 1.96-1.83 (m, 2H), 1.35 (d, *J* = 7.5 Hz, 3H). Peaks at 1.26 (bs) and 0.88 (m) are observed due to polyethylene. ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.4, 138.9, 132.1, 129.1, 128.7, 120.2, 65.8, 64.6, 45.4, 27.5, 19.5; IR (neat): 2966 (s), 2929 (s), 1718 (s), 1669 (w), 1653 (w), 1559 (w), 1491 (s), 1374 (m), 1263 (m), 1132 (s), 1091 (s), 1014 (s), 937 (m), 830 (m), 668 (s) cm^{-1}; HRMS (ESI+) calculated for $C_{13}H_{15}ClO$ *m/z* (M+H) 223.0890, obsd. 223.0888.

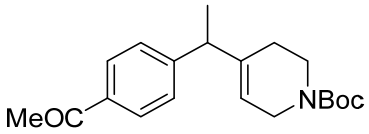
4-(1-(4-(trifluoromethyl)phenyl)ethyl)-3,6-dihydro-2H-pyran (**19m**):



19m

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 142 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 191 mg of vinyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19m**. The product was purified by silica gel flash chromatography by eluting with 1.5% EtOAc in hexanes to give product (only **19m**) as colorless oil in 65% yield (83 mg, 0.32 mmol), separable regioisomers (**19m:22m::3:1**), R_f = 0.3 (5% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 5.62-5.59 (m, 1H), 4.21-4.18 (m, 2H), 3.75-3.67 (m, 2H), 3.41 (q, J = 7.5 Hz, 1H), 1.95-1.87 (m, 2H), 1.39 (d, J = 7.5 Hz, 3H). Peaks at 1.26 (bs) and 0.88 (m) are observed due to polyethylene. ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.1, 138.6, 128.8 (q, $^2J_{CF}$ = 32.8 Hz), 128.1, 125.5 (q, $^3J_{CF}$ = 3.8 Hz), 124.5 (q, $^1J_{CF}$ = 272.2 Hz), 120.6, 65.8, 64.6, 45.9, 27.6, 19.4. Peaks at δ 30.5 and 29.9 are observed due to polyethylene. IR (neat): 2971 (s), 2835 (s), 1717 (w), 1618 (s), 1457 (m), 1417 (s), 1322 (s), 1161 (m), 1116 (s), 1069 (s), 1016 (m), 843 (s), 719 (w), 605 (m) cm^{-1}; HRMS (ESI+) calculated for $C_{14}H_{15}F_3O$ *m/z* (M+H) 257.1153, obsd. 257.1154.

Tert-butyl 4-(1-(4-acetylphenyl)ethyl)-5,6-dihydropyridine-1(2H)-carboxylate (**19n**):

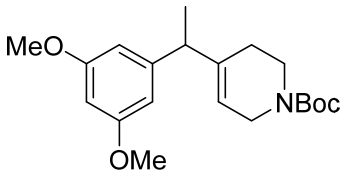


19n

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 123 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 166 mg of vinyl

triflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19n**. The product was purified by silica gel flash chromatography by eluting with 5% EtOAc in hexanes to give product as colorless oil in 55% yield (91 mg, 0.27 mmol), separable regioisomers (**19n:22n::10:1**), R_f = 0.3 (10% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.87 (m, 2H), 7.30-7.25 (m, 2H), 5.65-5.47 (m, 1H), 4.00-3.88 (m, 2H), 3.49-3.28 (m, 3H), 2.58 (s, 3H), 1.96-1.83 (m, 2H), 1.50 (s, 9H), 1.38 (d, *J* = 7.2 Hz, 3H). Peaks at 1.26 (bs) and 0.88 (m) are observed due to polyethylene. ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 150.6, 135.6, 128.7, 128.4, 127.9, 118.6, 115.7, 79.7, 46.1, 44.1, 43.7, 28.6, 27.5, 26.7, 19.4. Peak at δ 29.9 is observed due to polyethylene. IR (neat): 2974 (s), 2929 (m), 1681 (s), 1606 (s), 1570 (m), 1413 (m), 1364 (m), 1266 (s), 1156 (m), 1120 (w), 1015 (w), 957 (m), 844 (m), 667 (w), 599 (s); HRMS (ESI+) calculated for $C_{20}H_{27}NO_3$ *m/z* (M+Na) 352.1889, obsd. 352.1893.

Tert-butyl 4-(1-(3,5-dimethoxyphenyl)ethyl)-5,6-dihydropyridine-1(2H)-carboxylate (**19o**):

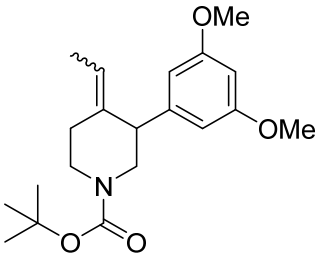


19o

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 136 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 166 mg of vinyl triflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19o**. The product was purified by silica gel flash chromatography by eluting with 5% EtOAc in hexanes to give product as colorless oil in

58% yield (101 mg, 0.29 mmol), separable regioisomers (**19o:22o::3:1**), R_f = 0.5 (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (d, *J* = 2.0 Hz, 2H), 6.30 (t, *J* = 2.0 Hz, 1H), 5.65-5.45 (m, 1H), 4.00-3.88 (m, 2H), 3.77 (s, 6H), 3.50-3.32 (m, 2H), 3.28 (q, *J* = 6.8 Hz, 1H), 1.83-2.00 (m, 2H), 1.50 (s, 9H), 1.33 (d, *J* = 7.2 Hz, 3H). Peaks at 1.26 (bs) and 0.88 (m) are observed due to polyethylene. ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 155.1, 147.6, 118.0, 115.2, 106.0, 97.9, 79.6, 55.4, 46.2, 43.7, 41.6, 28.6, 27.4, 19.6. Peak at δ 29.9 is observed due to polyethylene. IR (neat): 2972 (s), 2933 (w), 1692 (s), 1592 (s), 1456 (s), 1424 (s), 1365 (m), 1337 (m), 1240 (m), 1203 (m), 1151 (s), 1112 (s), 1058 (m), 939 (w), 831 (m), 698 (m), 668 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{20}H_{29}NO_4$ *m/z* (M+Na) 370.1994, obsd. 370.2002.

Tert-butyl 3-(3,5-dimethoxyphenyl)-4-ethylidenepiperidine-1-carboxylate (**22o**):

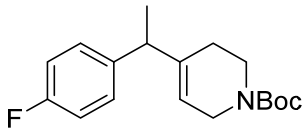


22o

The product is reported as a regioisomer of **19o**. It was purified by silica gel flash chromatography by eluting with 5% EtOAc in hexanes to give product as colorless oil in 14% yield (24 mg, 0.07 mmol), R_f = 0.5 (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.46-6.40 (m, 2H), 6.36-6.32 (m, 1H), 5.22-5.06 (m, 1H), 3.77 (s, 6H), 3.74-3.47 (m, 3H), 3.44-3.28 (m, 2H), 2.48-2.16 (m, 2H), 1.60 (d, *J* = 6.5 Hz, 3H), 1.45 (s, 9H). Peaks at 1.26 (bs) and 0.88 (m) are observed due to polyethylene. ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.8, 154.9, 143.5, 138.3, 120.0, 106.1, 98.3, 79.8, 55.5, 49.6, 28.7, 26.6, 13.1;

IR (neat): 2971 (m), 2933 (w), 1716 (s), 1496 (s), 1424 (s), 1340 (w), 1337 (m), 1242 (m), 1204 (m), 1152 (s), 1111 (s), 1065 (m), 993 (w), 828 (m), 668 (m) cm^{-1}.

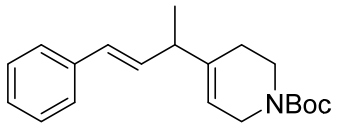
Tert-butyl 4-(1-(4-fluorophenyl)ethyl)-5,6-dihydropyridine-1(2H)-carboxylate (**19p**):



19p

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 105 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 166 mg of vinyl triflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19p**. The product was purified by silica gel flash chromatography by eluting with 5% EtOAc in hexanes to give product as colorless oil in 68% yield (104 mg, 0.34 mmol), separable regioisomers (**19p:22p::4:1**), R_f = 0.4 (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15-7.10 (m, 2H), 6.96 (t, J = 9.0 Hz, 2H), 5.60-5.40 (m, 1H), 3.98-3.86 (m, 2H), 3.50-3.30 (m, 3H), 1.96-1.80 (m, 2H), 1.45 (s, 9H), 1.34 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7 (d, $^1J_{CF}$ = 243.0 Hz), 155.2, 140.6 (d, $^4J_{CF}$ = 3.0 Hz), 140.4, 129.1 (d, $^3J_{CF}$ = 8.0 Hz), 118.3, 115.3 (d, $^2J_{CF}$ = 21.0 Hz), 79.6, 45.5, 43.6, 40.7, 28.7, 27.4, 19.8; IR (neat): 2970 (s), 2930 (m), 1692 (s), 1602 (w), 1508 (s), 1414 (s), 1364 (s), 1238 (m), 1157 (s), 1110 (s), 1014 (m), 981 (w), 836 (m), 667 (m) cm^{-1}; HRMS (ESI+) calculated for $C_{18}H_{24}FNO_2$ *m/z* (M+Na) 328.1689, obsd. 328.1685.

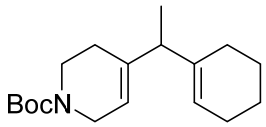
(*E*)-tert-butyl 4-(4-phenylbut-3-en-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (**19q**):



19q

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 111 mg of styryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 166 mg of vinyl triflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19q**. The product was purified by silica gel flash chromatography by eluting with 2% EtOAc in hexanes to give product as colorless oil in 80% yield (125 mg, 0.40 mmol), separable regioisomers (**19q:22q::2:1**). Yields are reported as a mixture of regioiosmers, R_f = 0.6 (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.27 (m, 4H), 7.24-7.18 (tt, *J* = 7.5, 1.5 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.12 (dd, *J* = 8.5, 7.0 Hz, 1H), 5.58-5.34 (m, 1H), 3.98-3.84 (m, 2H), 3.54-3.42 (m, 1H), 2.94 (m, 1H), 2.20-2.00 (m, 2H), 1.48-1.46 (s, 9H), 1.22 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 137.7, 134.0, 130.3, 129.4, 128.7, 127.3, 126.3, 126.1, 117.7, 79.6, 43.7, 37.1, 31.2, 28.7, 26.9, 18.4; IR (neat): 2973 (s), 2928 (m), 2863 (w), 1693 (s), 1600 (w), 1449 (s), 1365 (s), 1337 (w), 1240 (s), 1162 (s), 1113 (s), 965 (m), 863 (m), 750 (s), 693 (s), 668 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{20}H_{27}NO_2$ *m/z* (M+Na) 336.1939, obsd. 336.1943.

Tert-butyl 4-(1-(cyclohex-1-en-1-yl)ethyl)-5,6-dihydropyridine-1(2H)-carboxylate (**19r**):

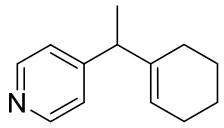


19r

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 232 mg of vinyl boronic acid pinacol ester (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 190 mg of cyclohexenyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **19r**. The product was purified by silica gel flash chromatography by eluting with 1% EtOAc in hexanes to give product as colorless oil in 72% yield (105 mg, 0.36 mmol), inseparable mixture of regioisomers (**19r:22r::6:1**), R_f = 0.6 (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.48-5.29 (m, 2H), 4.99 (q, *J* = 7.0 Hz, 1H) minor, 3.86 (t, *J* = 17.0 Hz, 2H), 3.50-3.33 (m, 2H), 2.59 (q, *J* = 7.0 Hz, 1H), 2.07-1.93 (m, 3H), 1.92-1.65 (m, 3H), 1.58-1.50 (m, 4H), 1.45 (s, 9H), 1.08 (d, *J* = 7.0 Hz, 3 H). Peak at δ 1.24 (bs) is due to polyethylene. ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.2, 139.7, 136.0, 128.5, 125.7, 121.8, 121.3, 117.6, 116.0, 79.6, 51.3, 47.7, 43.8, 40.3, 36.3, 35.8, 28.7, 28.6, 26.5, 25.6, 23.2, 22.9, 16.9. Additional peaks at 29.9 and 30.6 are due to polyethylene. IR (neat): 2974 (s), 2931 (m), 2860 (w), 1699 (s), 1601 (w), 1415 (m), 1366 (s), 1334 (m), 1303 (m), 1222(w), 1155 (s), 1115 (s), 1071 (w), 952 (w), 861 (m), 769 (m), 668 (m) cm^{-1}; HRMS (ESI+) calculated for $C_{18}H_{29}NO_2$ *m/z* (M+Na) 314.2096, obsd. 314.2099.

General procedure for the 1,1 vinylarylation of ethylene with hetroaromatic boronic esters

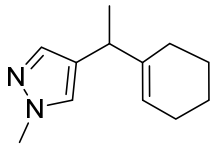
4-(1-(cyclohex-1-en-1-yl)ethyl)pyridine (**25a**):



25a

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 154 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 190 mg of vinyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **19a** was used to give **25a**. The product was purified by silica gel flash chromatography by eluting with 8% EtOAc in hexanes to give product as colorless oil in 85% yield (80 mg, 0.43 mmol), R_f = 0.1 (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (d, *J* = 6.5 Hz, 2H), 7.09 (d, *J* = 6.0 Hz, 2H), 5.61-5.56 (m, 1H), 3.25 (q, *J* = 7.0 Hz, 1H), 2.08-2.00 (m, 2H), 1.78-1.63 (m, 2H), 1.55-1.48 (m, 4H), 1.30 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 149.9, 139.9, 123.2, 122.4, 46.2, 27.1, 25.5, 23.1, 22.7, 19.0; IR (neat): 2966 (w), 2925 (s), 2856 (m), 1595 (s), 1558 (m), 1456 (m), 1411 (s), 1373 (w), 1070 (m), 1030 (m), 993 (m), 917 (m), 820 (s), 805 (w), 668 (m), 640 (w), 604 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{13}H_{17}N$ *m/z* (M+H) 188.1439, obsd. 188.1444.

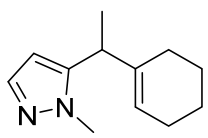
4-(1-(cyclohex-1-en-1-yl)ethyl)-1-methyl-1H-pyrazole (**25b**):



25b

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 156 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 190 mg of vinyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **25a** was used to give **25b** except that the reaction was run for 36 h instead of 16 h at 75 °C. The product was purified by silica gel flash chromatography by eluting with 8% EtOAc in hexanes to give product as colorless oil in 63% yield (60 mg, 0.32 mmol), R_f = 0.2 (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (s, 1H), 7.09 (s, 1H), 5.53-5.49 (m, 1H), 3.85 (s, 3H), 3.25 (q, *J* = 7.5 Hz, 1H), 2.08-1.98 (m, 2H), 1.94-1.78 (m, 2H), 1.60-1.51 (m, 4H), 1.28 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.8, 138.3, 128.0, 126.6, 120.7, 39.0, 37.6, 25.8, 25.5, 23.3, 22.9, 19.8; IR (neat): 2928 (s), 2856 (m), 1667 (s), 1445 (s), 1398 (m), 1373 (w), 1192 (m), 1169 (m), 985 (s), 850 (m), 668 (m) cm^{-1}; HRMS (ESI+) calculated for $C_{12}H_{18}N_2$ *m/z* (M+H) 191.1548, obsd. 191.1550.

5-(1-(cyclohex-1-en-1-yl)ethyl)-1-methyl-1H-pyrazole (**25c**):

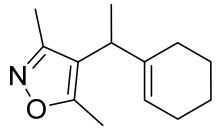


25c

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 156 mg of aryl boronic

acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 190 mg of vinyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **25b** was used to give **25c**. The product was purified by silica gel flash chromatography by eluting with 8% EtOAc in hexanes to give product as colorless oil in 50% yield (48 mg, 0.25 mmol), R_f = 0.2 (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 2.0 Hz, 1H), 6.05 (d, *J* = 1.5 Hz, 1H), 5.43-5.35 (m, 1H), 3.73 (s, 3H), 3.35 (q, *J* = 6.5 Hz, 1H), 2.04-1.96 (m, 2H), 1.94-1.70 (m, 2H), 1.62-1.50 (m, 4H), 1.38 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.8, 139.0, 137.9, 122.8, 104.4, 38.9, 36.6, 26.0, 25.4, 23.1, 22.7, 19.0; IR (neat): 2926 (s), 1733 (s), 1717 (m), 1652 (s), 1456 (s), 1395 (m), 1373 (w), 1201 (s), 928 (s), 778 (s), 668 (s) cm^{-1}; HRMS (ESI+) calculated for $C_{12}H_{18}N_2$ *m/z* (M+H) 191.1548, obsd. 191.1550.

4-(1-(cyclohex-1-en-1-yl)ethyl)-3,5-dimethylisoxazole (**25d**):

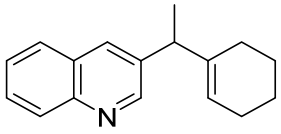


25d

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 167 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 190 mg of vinyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **25b** was used to give **25d**. The product was purified by silica gel flash chromatography by eluting with 5% EtOAc in hexanes to give product as colorless oil in 52% yield (53 mg, 0.26 mmol), R_f = 0.6 (15% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55-5.51 (m, 1H), 3.08 (q, *J* = 7.0 Hz, 1H), 2.29 (d, *J* = 2.0 Hz, 3H), 2.16 (d, *J*

= 2.0 Hz, 3H), 2.09-2.01 (m, 2H), 1.82-1.74 (m, 2H), 1.62-1.50 (m, 4H), 1.28 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.7, 159.9, 138.6, 121.0, 116.2, 35.3, 28.0, 25.4, 23.2, 22.7, 18.0, 11.6, 10.9; IR (neat): 2918 (s), 2849 (m), 1734 (s), 1699 (s), 1652 (s), 1575 (m), 1558 (s), 1540 (m), 1456 (s), 1259 (m), 1036 (m), 800 (m), 668 (m) cm^{-1}; HRMS (ESI+) calculated for $C_{13}H_{19}NO$ *m/z* (M+H) 206.1545, obsd. 206.1537.

3-(1-(cyclohex-1-en-1-yl)ethyl)quinoline (**25e**):

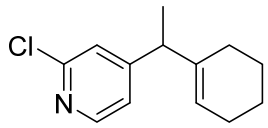


25e

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 191 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 190 mg of vinyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The same procedure used for the synthesis of **25b** was used to give **25e**. The product was purified by silica gel flash chromatography by eluting with 7% EtOAc in hexanes to give product as colorless oil in 89% yield (105 mg, 0.44 mmol), R_f = 0.3 (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.79 (d, *J* = 2.0 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.64 (dt, *J* = 8.5, 1.5 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 5.69-5.65 (m, 1H), 3.51 (q, *J* = 7.0 Hz, 1H), 2.12-2.04 (m, 2H), 1.87-1.74 (m, 2H), 1.59-1.51 (m, 4H), 1.46 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.1, 147.2, 140.3, 138.6, 133.2, 129.4, 128.8, 128.4, 127.7, 126.7, 122.4, 44.5, 27.2, 25.6, 23.2, 22.7, 19.5; IR (neat): 2965 (w), 2924 (s), 2855 (m), 1570 (m), 1493 (s), 1448 (s), 1437 (w), 1378 (m), 1333 (m), 1260 (w), 1122 (m), 1027 (m), 969 (m), 905 (s), 787 (s0, 749 (s), 668 (m) cm^{-1}; HRMS (ESI+)

calculated for $C_{17}H_{19}N$ *m/z* (M+H) 238.1596, obsd. 238.1597.

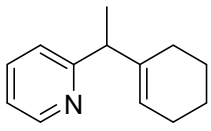
2-chloro-4-(1-(cyclohex-1-en-1-yl)ethyl)pyridine (**25f**):



25f

To a 10 mL Schlenk bomb equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 180 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 190 mg of vinyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **25b** was used to give **25f**. The product was purified by silica gel flash chromatography by eluting with 5% EtOAc in hexanes to give product as colorless oil in 74% yield (82 mg, 0.37 mmol), R_f = 0.4 (10% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 5.2 Hz, 1H), 7.15 (s, 1H), 7.06 (dd, *J* = 5.2, 1.2 Hz, 1H), 5.65-5.59 (m, 1H), 3.28 (q, *J* = 6.8 Hz, 1H), 2.11-2.02 (m, 2H), 1.82-1.66 (m, 2H), 1.61-1.52 (m, 4H), 1.33 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 151.9, 149.6, 139.3, 123.5, 123.1, 122.0, 46.1, 29.9 (PE), 27.1, 25.5, 23.1, 22.6, 18.9; IR (neat): 2923 (s), 2854 (m), 1589 (s), 1544 (m), 1462 (m), 1385 (s), 1123 (w), 1086 (s), 831 (m), 714 (m), 668 (m) cm^{-1}; HRMS (ESI+) calculated for $C_{13}H_{16}ClN$ *m/z* (M+H) 222.1050, obsvd. 222.1048.

2-(1-(cyclohex-1-en-1-yl)ethyl)pyridine (**25g**):



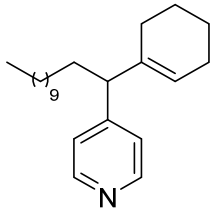
25g

To a 10 mL Schlenk bomb equipped with a stir bar, was added 129 mg of CsF (0.85

mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 276 mg of 2-(tributylstannyl)pyridine (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 190 mg of vinyl nonaflate (0.5 mmol, 1.0 equiv) and 5 mL of DMA. The general procedure used for the synthesis of **25a** was used to give **25g**. After the reaction time, the reaction mixture was cooled to room temperature and then filtered through celite with ether (1x20 mL). Next, 20 mL of 20% aqueous KOH solution was added to the filterate and stirred for 1 h. The solution was then diluted with 100 mL of ether and transferred to a separatory funnel and washed with H_2O (3x30 mL) followed by brine (1x10 mL). The organic layer was then dried over anhydrous Na_2SO_4. After filtration, the solvents were removed via rotary evaporation. The product was purified by silica gel flash chromatography by eluting with 5% EtOAc in hexanes to give product as colorless oil in 70% yield (66 mg, 0.35 mmol), R_f = 0.3 (10% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 4.0 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.6, 1H), 7.08 (t, *J* = 6.4 Hz, 1H), 5.63-5.57 (m, 1H), 3.50 (q, *J* = 6.4 Hz, 1H), 2.11-2.03 (m, 2H), 1.86-1.78 (m, 2H), 1.61-1.52 (m, 4H), 1.40 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 149.2, 140.6, 136.4, 121.9, 121.8, 121.2, 49.2, 29.9 (PE), 27.4, 25.6, 23.2, 22.8, 18.6. IR (neat): 2963 (w), 2924 (s), 2855 (m), 1717 (w), 1587 (s), 1568 (m), 1471 (s), 1447 (w), 1430 (s), 1367 (w), 1147 (m), 1029 (m), 917 (m), 793 (m), 747 (s), 668 (s) cm^{-1}; HRMS (ESI+) calculated for $C_{13}H_{17}N$ *m/z* (M+H) 188.1439, obsvd. 188.1433.

Procedure for the 1,1-vinylarylation of dodecene

4-(1-(cyclohex-1-en-1-yl)butyl)pyridine (**26**):



26

To a 20 mL disposable vial equipped with a stir bar, was added 71 mg of $NaHCO_3$ (0.85 mmol, 1.7 equiv), 18 mg of dba (0.075 mmol, 0.15 equiv), 154 mg of aryl boronic acid (0.75 mmol, 1.5 equiv), 23 mg of $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 190 mg of vinyl nonaflate (0.5 mmol, 1.0 equiv), 84 mg of dodecene (0.5 mmol, 1.0 equiv.) and 5 mL of DMA. The vial was sealed under nitrogen and reaction was run for 16 h at 55 °C. The work up procedure for the synthesis of **19a** was used for **26**. The product was purified by silica gel flash chromatography by eluting with 14% EtOAc in hexanes to give product as colorless oil in 65% yield (106 mg, 0.32 mmol), R_f = 0.3 (20% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (d, J = 4.8 Hz, 2H), 7.11 (d, J = 5.7 Hz, 2H), 5.61-5.56 (m, 1H), 3.07 (t, J = 7.8 Hz, 1H), 2.08-2.00 (m, 2H), 1.82-1.60 (m, 4H), 1.55-1.48 (m, 4H), 1.34-1.18 (m, 18H), 0.87 (t, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 149.7, 138.9, 123.6, 123.0, 52.7, 32.1, 32.0, 29.8, 29.7, 29.6, 27.9, 26.6, 25.6, 23.1, 22.9, 22.7, 14.3; IR (neat): 2921 (w), 2852 (s), 1594 (s), 1558 (m), 1457 (m), 1412 (s), 1373 (w), 1070 (m), 1030 (m), 993 (m), 917 (m), 820 (s), 668 (m), 650 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{23}H_{37}N$ *m/z* (M+H) 328.3004, obsvd. 328.3013.

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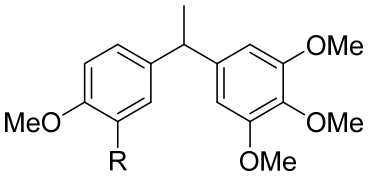
CHAPTER 3

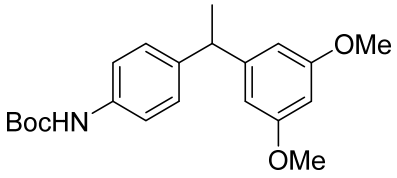
PALLADIUM-CATALYZED 1,1-DIARYLATION OF ETHYLENE

Introduction

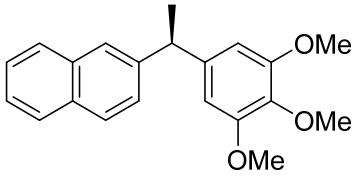
The 1,1-diarylalkane substructure is an important structural motif, as it is found in a wide array of molecules exhibiting various biological properties such as antiviral,[1] anticancer,[2-4] antihistamine,[5,6] and antiasthmatic activity,[7] as shown in Figure 3.1. Among them, diarylmethines containing two different aryl groups are particularly interesting as the presence of the methyl group in these drug molecules increases their binding affinity, thus improving efficacy.[8] For example, **A** is an antilung cancer agent with GI_{50} value of 28 nM against HCT-116 cell line. Similarly, C-6 is an antibreast cancer agent with EC_{50} value of 11 μM against MCF-7 cancer cell line. It is active against patient-derived metastatic and chemoresistant breast cancer cells. Additionally, minimal cell death is observed in patient-derived nontumorigenic cells making it a highly selective molecule. As a result of the importance of diarylmethine motif, significant efforts have been devoted to their efficient synthesis, including enantioselective hydrogenation of 1,1-diarylalkenes,[9-12] rhodium-catalyzed Tsuji-Wilkinson decarbonylation,[13] and enantiospecific metal-catalyzed cross-coupling reactions.[14,15] In this chapter, transition-metal-catalyzed approaches to access a diverse range of 1,1-diarylmethine derivatives are discussed.



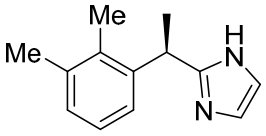
A, Isoerianin
R = OH, anti-lung cancer agent, GI_{50} = 28 nM (HCT-116);
B, R = H, anti-viral agent
IC_{50} = 5.6 μM (VacV-GFP)



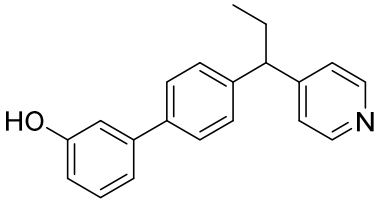
C, C-6
anti-breast cancer agent
EC_{50} = 11 μM (MCF-7)



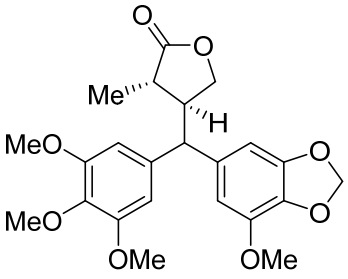
D, anti-cancer agent



E, Demiditraz
a pesticide



F, anti-prostate cancer agent
IC_{50} = 189 nM (CYP17)



G, Peperomin B
anti-inflammatory

Figure 3.1. Examples of bioactive 1,1-diarylalkanes.

Background

Many different attractive approaches have been reported to access 1,1-diarylmethine derivatives. A highly efficient route is the transition-metal-catalyzed cross-coupling of various electrophiles, such as benzylic halides and ethers with Grignard, organozinc, and organoboron reagents (Figure 3.2). The use of benzylic electrophiles in these reactions is challenging due to their slow rate of oxidative addition, and the propensity of metal-alkyl species to rapidly undergo β-hydride elimination. In 2009, Carretero and co-workers reported a Pd-catalyzed Kumada-Corriu cross-coupling of benzylic bromide **1** with an aryl Grignard reagent **2** to afford 1,1-diarylmethine **3** in excellent yield (Figure 3.2a).[16] Recently, Jarvo and co-workers reported a stereospecific cross-coupling of benzylic ether **4** with excess of methyl magnesium iodide under Ni(0)-catalysis to form 1,1-diarylmethine **5** in excellent yield and complete retention of stereochemistry (Figure 3.2b).[14,15] The synthesis of enantioenriched starting material 1,1-diarylether **4** was achieved by organocatalyzed enantioselective 1,2-addition of phenyl boronic acid to 2-naphthaldehyde, followed by methylation of alcohol in the presence of sodium hydride. Subsequently, Watson and co-workers reported a nickel-catalyzed cross-coupling of benzylic pivalate **6** with phenyl boroxine to form **5** in 89% yield with complete retention of configuration (Figure 3.2c).[17] The enantioenriched starting material **6** was synthesized using enantioselective 1,2-addition of dimethyl zinc to 2-naphthaldehyde.

An alternate approach involves cross-coupling of aryl electrophiles with enantioenriched benzylic transmetallating agents to form 1,1-diarylalkanes with retention of configuration (Figure 3.3). One of the earliest protocols, developed by Hiyama and co-workers, involved the Pd(0)-catalyzed cross-coupling of an aryl triflate with a benzylic

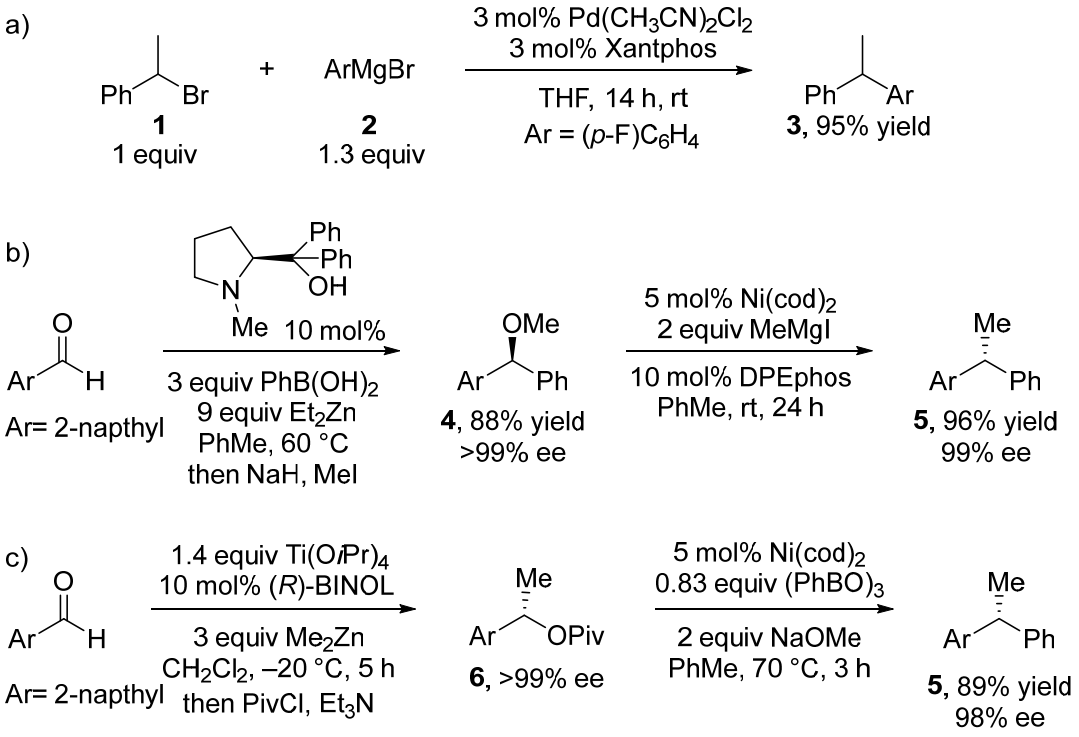


Figure 3.2. Cross-coupling of benzylic electrophiles with aryl/alkyl nucleophiles. a) Pd-catalyzed cross-coupling of benzylic bromide from Carretero and co-workers, 2009. b) Ni-catalzed cross-coupling of benzylic ether from Jarvo and co-workers, 2011. c) Ni-catalyzed cross-coupling of benzylic pivalate from Watson and co-workers, 2013.

trifluorosilane **7**, which was obtained from hydrosilylation of styrene followed by fluorination, to generate diarylmethine **8** in a modest yield of 31-51% and complete retention of stereochemistry (Figure 3.3a).[18] Recently, Crudden and co-workers reported a Suzuki cross-coupling of an aryl iodide with a chiral organoborane **9** to access an enantioenriched diarylmethine **10** in 62% yield and 90% retention of configuration (Figure 3.3b).[19] The chiral organoborane **9** was obtained by the rhodium-catalyzed enantioselective hydroboration of styrene. Despite the significant advancement in the stereospecific cross-coupling of benzylic reagents, there are several drawbacks that need to be addressed, including poor functional group tolerance and the presynthesis of

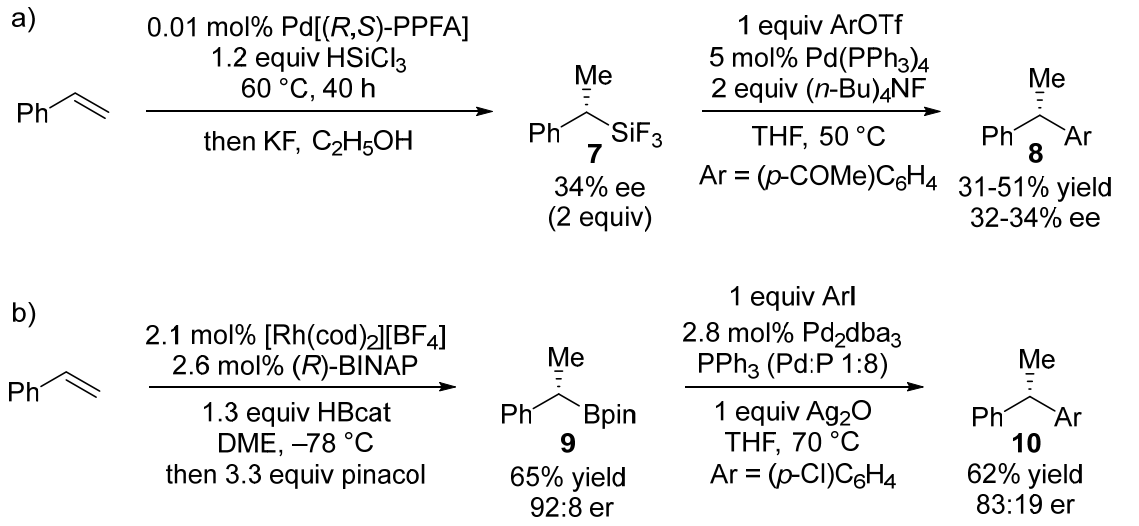


Figure 3.3. Cross-coupling of aryl electrophiles with chiral benzylic transmetallating agents. a) Pd-catalyzed cross-coupling of benzylic trifluorosilane from Hiyama and co-workers, 1990. b) Pd-catalyzed cross-coupling of benzylic boronic acid pinacol ester from Crudden and co-workers, 2009.

enantioenriched reagents.

In 2013, Fu and co-workers reported a one-pot two-step protocol for the enantioselective synthesis of 1,1-diarylalkanes using Ni(0) and a chiral ligand (Figure 3.4).[20] For example, racemic benzyl alcohol **11** was converted to a benzyl mesylate, followed by Negishi cross-coupling with an aryl zinc reagent to form a 1,1-diarylmethane **12** in excellent yield and good ee. The use of excess of LiI was crucial for the success of the reaction. It was hypothesized that the benzylic mesylate was converted to a benzylic iodide *in situ*, which underwent nickel-catalyzed cross-coupling reaction.

In 2007, Sigman and co-workers reported an alternate approach for a one-pot synthesis of 1,1-diarylmethines, which involved reductive Heck-type reaction of styrenes with aryl cross-coupling partners (Figure 3.5).[21] For example, a palladium-catalyzed reaction between styrene **13** and phenyl tributyltin **14** afforded 1,1-diarylmethine **15** in

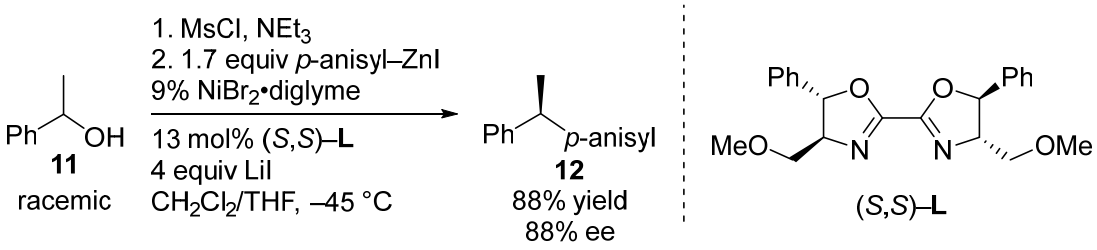


Figure 3.4. One-pot two-step enantioselective synthesis of 1,1-diarylalkanes as developed by Fu and co-workers in 2013.

76% yield. Mechanistically, the initial oxidation of isopropanol transfers a hydride to Pd(II) to form a Pd–H intermediate **A**. Alkene coordination is followed by migratory insertion to form a Pd-benzyl species **C**, which presumably exists as a stable π-benzylpalladium intermediate. Then, this undergoes transmetallation with **14** followed by reductive elimination to generate the desired product **15**. The catalytic cycle is closed by oxidation of Pd(0) back to Pd(II) using oxygen. The use of MnO_2 as an additive decomposes the hydrogen peroxide formed during the regeneration of Pd(II), whose presence could otherwise be problematic. The major limitation of this reaction (*i.e.*, the use of toxic tributyltin reagents) was later circumvented by the use of environmentally friendly and commercially available aryl boronic esters. For example, the reaction of styrene **13** with phenyl boronic ester **16** led to the corresponding product **15** in 81% yield.[22]

As discussed above, significant efforts have been devoted to the efficient synthesis of 1,1-diarylalkanes. Although enantioselective, the cross-coupling approach suffers from major drawbacks, such as harsh conditions, poor functional group tolerance, and pre-synthesis of substrates. Other approaches such as the method developed by our group, require strongly oxidative conditions, which makes the process synthetically less attractive. Therefore, to access a diverse range of 1,1-diarylalkanes through olefin functionalization,

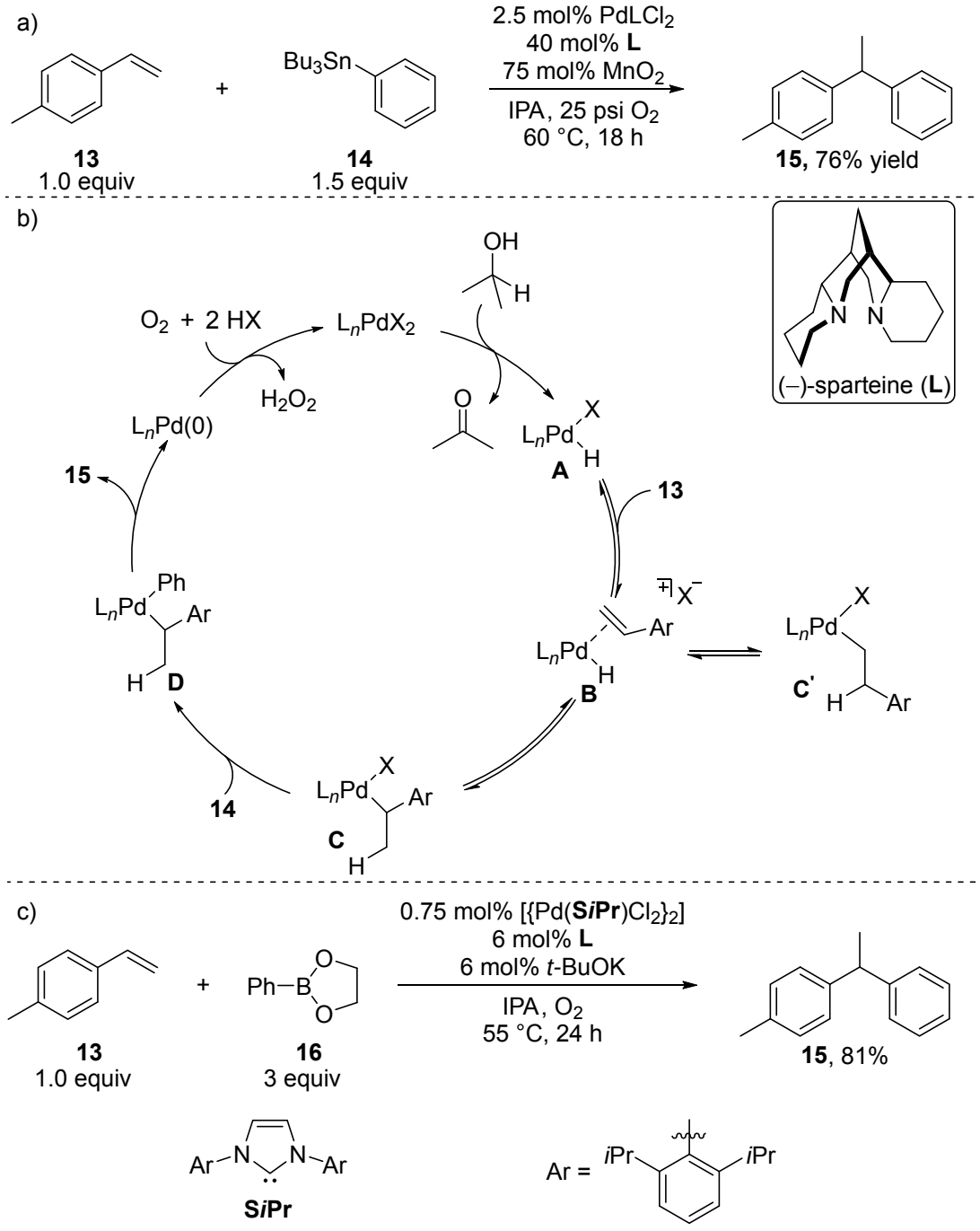


Figure 3.5. Reductive Heck approach for the one step synthesis of 1,1-diarylalkanes as developed by Sigman and co-workers in 2007. a) General reaction. b) Proposed mechanism. c) Reaction with boronic ester.

a Pd(0)-catalyzed approach has been developed that allows the 1,1-diarylation of ethylene with aryl diazonium and aryl boronic acid derivatives in an efficient manner.[23]

Results and Discussion

As discussed in Chapter 2, we have discovered a unique method of difunctionalizing one end of ethylene with two different groups. This process involved the formation of a stable π-allylpalladium species, which can be further functionalized using different nucleophiles to form complex molecules from simple starting materials.[24] Along the same lines, we envisioned expanding the scope of this transformation beyond vinyl electrophiles to include aryl diazonium salts as electrophiles.[23] They were chosen as electrophiles because of their ability to rapidly undergo oxidative addition. Also, the Pd-aryl species thus formed are electrophilic, which is crucial for the success of the reaction. Their use in three-component cross-coupling reactions would allow for rapid construction of a wide variety of biologically relevant 1,1-diarylmethine motifs.

Mechanistically, the first step involves the oxidative addition of an aryl diazonium salt **17** to a Pd(0) catalyst to form a Pd(II)-aryl adduct **A** (Figure 3.6). The noncoordinating counterion (*i.e.*, tetrafluoroborate) renders **A** electrophilic, which should enhance ethylene coordination and migratory insertion rather than transmetallation, to form a Pd(II)-alkyl intermediate **B**. This intermediate undergoes β-hydride elimination and then reinsertion into the styrene to form π-benzylpalladium species **D**. Base-assisted transmetallation is followed by a reductive elimination pathway to form a 1,1-diarylated product **19**. Of note is that after the first β-hydride elimination, the Pd–H can dissociate from the diene to form an undesired Heck product. However, presumably the electrophilic nature of the catalyst

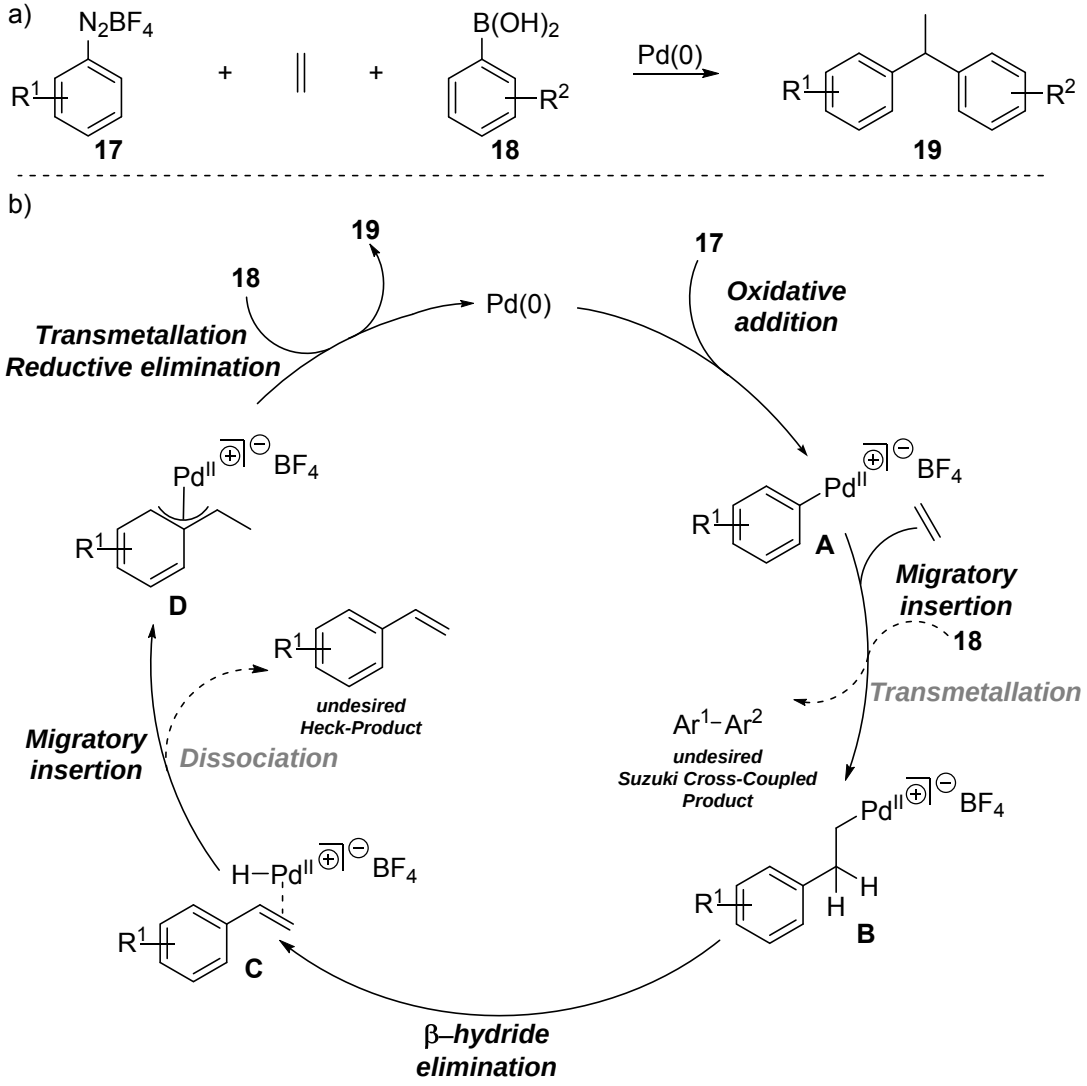


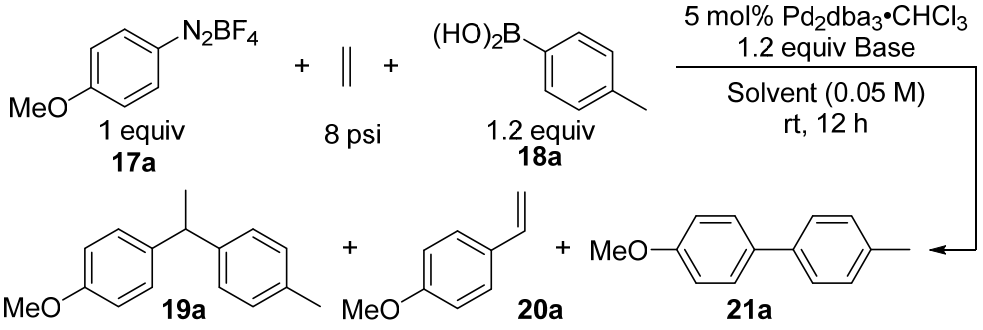
Figure 3.6. Palladium-catalyzed 1,1-diarylation of ethylene with aryl diazonium salts and aryl boronic acids. a) General reaction. b) Proposed mechanism.

will facilitate styrene coordination rather than dissociation.

In our initial investigation, ethylene, *para*methoxyphenyl diazonium tetrafluoroborate and *para*methylphenyl boronic acid was subjected to the reaction conditions previously reported by our group for 1,1-vinylarylation of ethylene (Table 3.1, entry 1).[23] However, only the Heck product was observed. The use of less coordinating solvent such as THF and lowering the pressure of ethylene from 15 psi to 8 psi afforded the desired three-component product in 4% yield as detected by gas chromatography, albeit the Heck product was the major byproduct (entries 2-3). Further improvement in the yield was observed by changing the solvent to *tert*-amyl alcohol and the base to potassium phosphate (entries 4-5). Increasing the temperature of the reaction to 80 ^{o}C gave 65% of the three-component product along with the Heck and Suzuki byproducts (entries 6-7). The best result was obtained when the solvent was changed to *tert*-butanol, which gave 75% yield of **19a** using 2 mol% catalytic loading and within 4 h (entries 8-9). It should be noted that when *tert*-butanol was used, both K_3PO_4 and $NaHCO_3$ gave similar results (entries 8-9).

Under the optimized conditions, the scope of the 1,1-difunctionalization reaction of ethylene with different aryl diazonium salts and aryl boronic acids was explored (Figure 3.7). A wide range of electron donating substituents such as methyl (**19a**), hydroxyl (**19b**), and isopropoxy (**19c**) in the *para*position afforded the desired product in good yields. Additionally, substitution at the *meta*position, such as halogens (**19c**, **19f**), a secondary amide (**19e**) and an aldehyde (**19g**), is well tolerated under the reaction conditions. The compatibility of challenging functional groups on the arene such as a nitro group (**19h**) is particularly interesting as it provides a handle for further functionalization. Sterically

Table 3.1. Optimization for the 1,1-diarylation of ethylene with *para*methoxyphenyl diazonium tetrafluoroborate and *para*methyphenyl boronic acid



Entry	Base	Solvent	Yield of **19a** (%)[a]	Ratio **19a**:**20a**:**21a**
1[b]	$NaHCO_3$	DMA	0	**20a** only
2[b]	$NaHCO_3$	THF	trace	**20a** only
3	$NaHCO_3$	THF	4	7:87:6
4	$NaHCO_3$	^{t}AmOH	33	33:66:1
5	K_3PO_4	^{t}AmOH	41	47:47:6
6[c]	K_3PO_4	^{t}AmOH	50	67:27:6
7[d]	K_3PO_4	^{t}AmOH	65	70:23:7
8[d,e,f]	K_3PO_4	^{t}BuOH	75	83:10:7
9[d,e,f]	$NaHCO_3$	^{t}BuOH	70	86:11:3
10[d,e,f]	$NaHCO_3$	^{t}AmOH	60	74:24:2

a) Determined by gas chromatography using an internal standard. b) Reaction performed at 15 psi. c) Reaction performed at 55 °C. d) Reaction performed at 80 °C. e) 2 mol% of Pd_2dba_3•$CHCl_3$ used. f) Reaction run for 4 h.

hindered 1- and 2-napthyl boronic acids (**19i**, **19j**) also served as effective coupling partners. Electron-deficient aryl diazonium salts such as 4-acetyl phenyl diazonium tetrafluoroborate (**19k**) afforded the product in moderate yield. Also, oxygen-containing heteroaromatic boronic acid (**19l**, **19m**) such as dibenzofuran gave good yield of the corresponding product. The scope of the reaction in terms of olefin partners has also been extended to allylic carbonates in collaboration with Dr. Longyan Liao, a previous graduate student in our laboratory (Figure 3.8). For example, the reaction of allyllic carbonate with

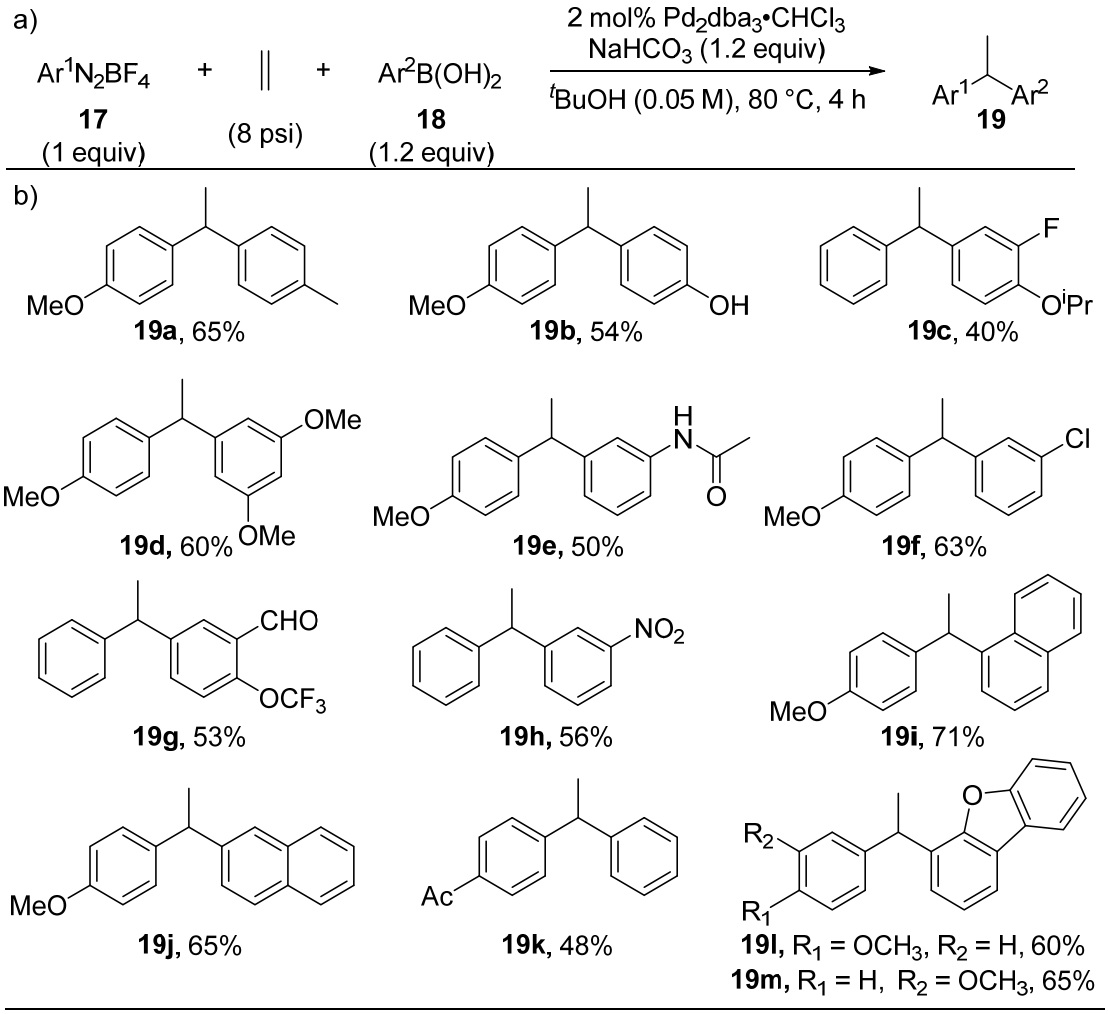


Figure 3.7. Diarylation of ethylene with aryl diazonium salts and aryl boronic acids. a) General reaction. b) Scope of the reaction.

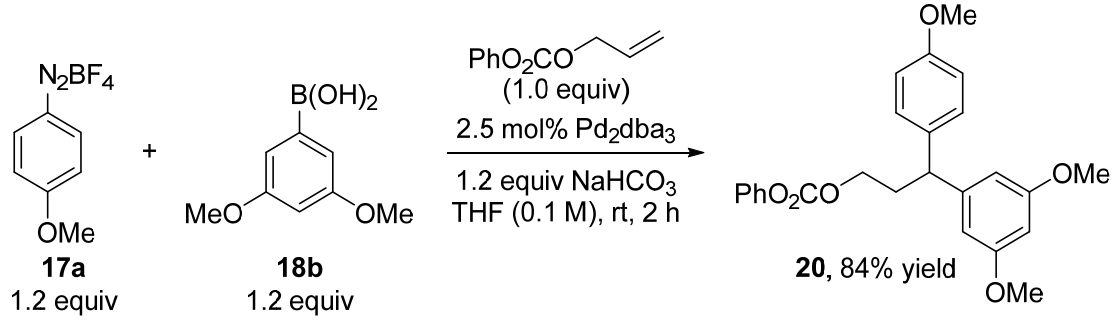


Figure 3.8. Palladium-catalyzed 1,1-diarylation of allyllic carbonate with an aryl diazonium salt and an aryl boronic acid.

aryl diazonium salt **17a** and an aryl boronic acid **18b** gave 84% yield of the 1,1-diarylated product **20**.

Mechanistic Studies

In order to study the mechanistic aspects of the reaction, deuterium labeling experiments were performed in collaboration with Dr. Ranjan Jana, a previous post-doctoral scholar in our laboratory (Figure 3.9). When isotopically labeled substrate **23** was subjected to the reaction conditions, 95% deuterium migration was observed. This suggests that the first migratory insertion positions palladium on the internal carbon of alkene **23**, which then undergoes β-hydride elimination followed by migratory insertion to form π-benzylpalladium intermediate similar to that shown in Figure 3.6. Also, when two different alkenes (*i.e.*, **23** and **23'**) reacted with *para*methoxyphenyl diazonium tetrafluoroborate and phenyl boronic acid in the same pot, no cross-over was observed. This suggests that the Pd–H species does not dissociate from alkene prior to the migratory insertion.

Negative Results

Apart from aryl diazonium salts, other potential electrophiles, such as aryl triflates, failed to give the desired three-component product. As shown in Table 3.2, aryl triflate **26** was screened using various phosphine ligands, however, only Heck (**28**) and Suzuki cross-coupled (**27**) products were observed. Although ethylene and allylic carbonates gave 1,1-difunctionalization products in synthetically useful yields, simple terminal olefins were not tolerated under the reaction conditions (Figure 3.10). For example, the reaction of 5-hexen-

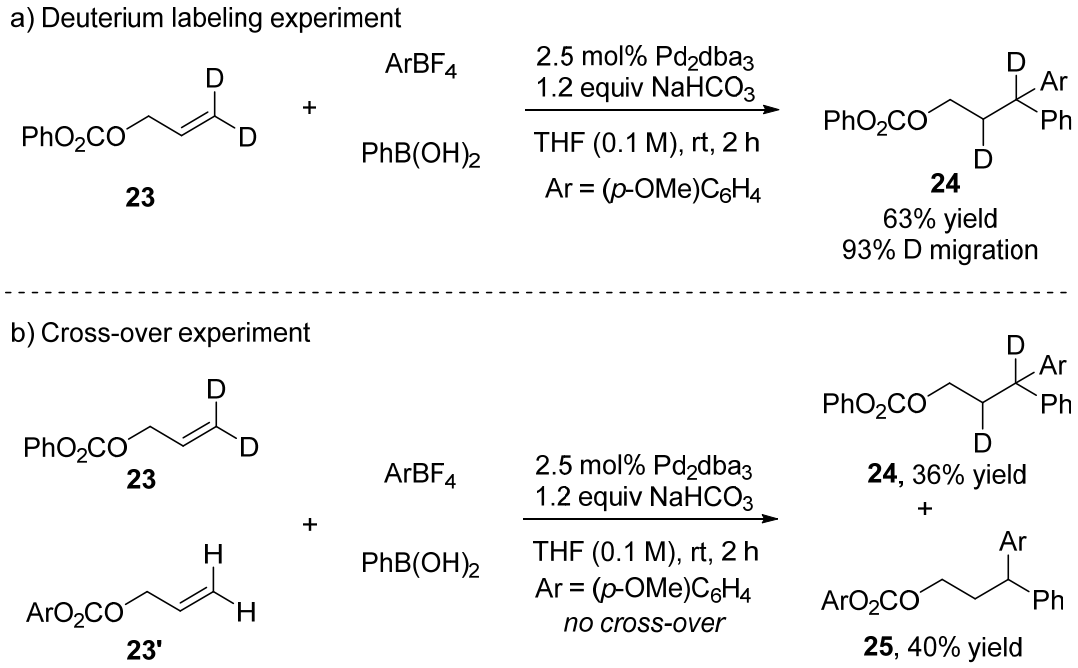


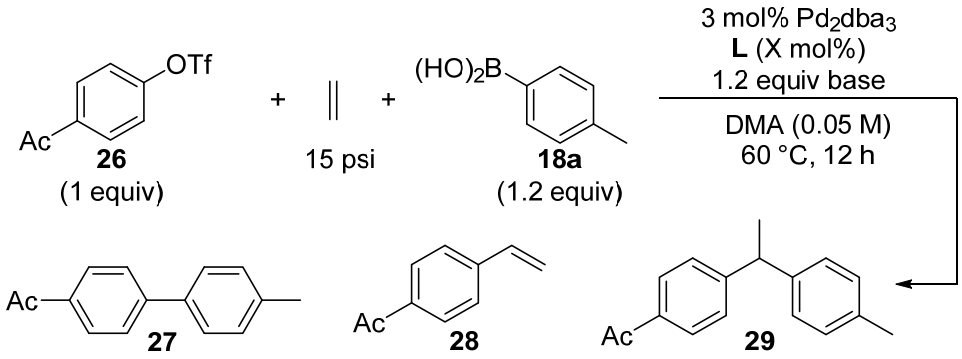
Figure 3.9. Mechanistic studies on palladium-catalyzed 1,1-diarylation of allylic carbonate. a) Deuterium labeling experiment. b) Cross-over experiment.

2-one with phenyl diazonium tetrafluoroborate and *para*methoxyphenyl boronic acid under the reaction conditions gave the Heck product and mixture of its isomers. The probable reason could be that the π-benzylpalladium intermediate is not stable enough to prevent migration along the alkyl chain through sequential β-hydride elimination and migratory insertion, thus leading to alkene isomers.

Conclusion

We have developed a palladium-catalyzed one-step three-component protocol for the 1,1-diarylation of ethylene with aryl diazonium salts and aryl boronic acids that leads to the installation of two different aryl groups across one end of the alkene. This protocol provides direct access to biologically relevant diarylmethine motifs in good to excellent

Table 3.2. Screening of an aryl triflate as an electrophile using various phosphine ligands



entry	**L** (X mol%)	base	% conv of **26**[a]	% yield of **27**[a]
1	PPh_3 (12)	$NaHCO_3$	50	28
2	PCy_3 (12)	$NaHCO_3$	100	90
3	P(*n*-Bu)$_3$ (12)	$NaHCO_3$	48	10
4	P(o-tolyl)$_3$ (12)	$NaHCO_3$	44	19
5	P(p-tolyl)$_3$ (12)	$NaHCO_3$	80	40
6	P(^{t}Bu)$_3$ (12)	KF	64	10
7[b]	dppf (6)	KF	100	0
8	Xanthphos (6)	KF	64	49

a) Determined by GC using an internal standard. b) 90% of **28** was observed. *Note:* **28** and **29** were not observed unless mentioned otherwise.

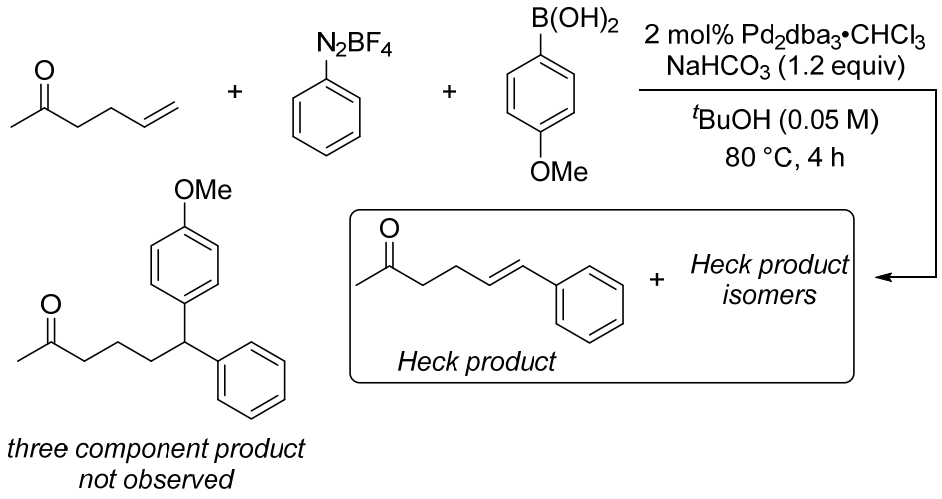


Figure 3.10. Palladium-catalyzed reaction of 5-hexen-2-one with phenyl diazonium tetrafluoroborate and *para*methoxyphenyl boronic acid.

yields from simple and easily accessible starting materials. This methodology has also been extended to include allylic carbonates as the olefin source.

Experimental

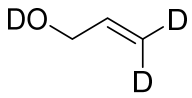
General considerations

THF was passed through an alumina column (Innovative Technology®) solvent system. Dimethylacetamide (DMA), ^{t}AmOH and ^{t}BuOH were used as purchased from Sigma-Aldrich (anhydrous, 99.8%, water < 0.005%). Ethylene was used as purchased from Sigma-Aldrich (≥ 99.5 % purity). All other reagents were obtained from commercial sources and used without further purification unless otherwise mentioned. Tris(dibenzylideneacetone)dipalladium[25] and Tris(dibenzylideneacetone)dipalladium-chloroform adduct[26] were prepared according to the reported procedure. Aryl diazonium salts were prepared according to the reported procedure.[27] ^{1}H NMR spectra were obtained at 300 MHz, 400 MHz or 500 MHz, chemical shifts are reported in ppm, and referenced to the $CHCl_3$ singlet at 7.26 ppm or CD_2Cl_2 at 5.33 ppm. ^{13}C NMR spectra were obtained at 75 MHz, 100 MHz or 126 MHz and referenced to the center line of the $CDCl_3$ triplet at 77.23 ppm or CD_2Cl_2 quintet at 54.20 ppm. The abbreviations s, d, t, q, dd, dt, sep, and m stand for the resonance multiplicities singlet, doublet, triplet, quartet, doublet of doublets, doublet of triplets, septet and multiplet, respectively. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with solvents indicated, visualized by a 254 nm UV lamp and stained with phosphomolybdic acid. Flash chromatography was performed using EM reagent silica 60 (230-400 mesh). IR spectra were recorded using a Thermo Nicolet FT-IR. High resolution mass spectrometry (HRMS) data were obtained

on a Waters LCP Premier XE instrument by ESI/TOF. Achiral GC (gas chromatography) was performed using a Hewlett Packard HP 6890 series GC system fitted with an Agilent HP-5 column. *Note:* The ^{1}H NMR and ^{13}C NMR spectra of unknown compounds can be obtained through Marriot Library.

Preparation of starting materials

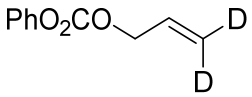
Prop-2-en-3,3-d_2-1-ol-d (**30**):



30

The compound **30** was prepared following the reported literature procedure.[28] Due to its volatile nature, it was taken to the next step without further purification.

Allyl-3,3-*d*$_2$-1-phenylcarbonate (**23**):



23

A reported procedure was followed for the synthesis of **23**.[29] To a CH_2Cl_2 solution (20 mL) of **30** (610 mg, 10.0 mmol, 1.0 equiv) was added pyridine (1.6 mL, 20 mmol, 2.0 equiv) and phenyl chloroformate (1.9 mL, 15.0 mmol, 1.5 equiv) at 0 °C, and the mixture was stirred at 0 °C for 5 min followed by warming to room temperature and allowing to stir overnight. To workup, the mixture was washed with water, and the resulting organic phase was dried over anhydrous Na_2SO_4. Solvents were evaporated *in vacuo*. The crude mixture was purified by column chromatography using 5% EtOAc in hexanes to give compound **23** in 77% yield as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.36

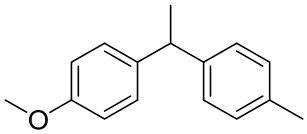
(m, 2H), 7.25 (dt, *J* = 7.2, 1.5 Hz, 1H), 7.19 – 7.17 (m, 2H), 5.98 (dt, *J* = 2.5, 1.3 Hz, 1H), 5.41 (td, *J* = 2.5, 1.4 Hz, 0.06 H), 5.32 – 5.29 (m, 0.04 H), 4.73 (dd, *J* = 5.8, 3.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 151.3, 131.1, 129.7, 126.2, 121.2, 69.3; IR (neat) 1754, 1592, 1492, 1373, 1232, 1202, 1021, 936, 686 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{10}H_9D_2O_3$.: 181.0834, obsd.: 181.0837.

General procedure for the optimization of 1,1-diarylation of ethylene with aryl diazonium salt and aryl boronic acid

The general procedure A, described below, was used with the following modifications. The reaction was performed on 0.10 mmol scale with ~ 10 wt% tetradecane used as an internal standard. After the required reaction time, the reaction mixture was passed through a small celite pipet with ethyl acetate and anaylzed for product formation by gas chromatography. The modifications described in Table 3.1 were applied in order to optimize the reaction.

General procedure A for the 1,1-diarylation of ethylene (Table 3.2)

1-methoxy-4-(1-(p-tolyl)ethyl)benzene (**19a**):

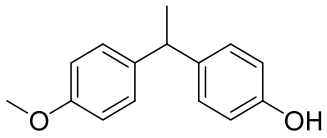


19a

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 82 mg of 4-tolyl boronic acid (0.60 mmol, 1.2 equiv), 10 mg of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.01 mmol, 0.02 equiv), 111 mg of 4-methoxyphenyl diazonium

tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The thick-wall Schlenk bomb was then evacuated followed by pressurization with ethylene at 8 psi at room temperature using a three way adapter. This process was repeated three times and the glass bomb was sealed with Teflon stopcock. The reaction mixture was stirred during the process of evacuation and pressurization. The reaction mixture was then heated to 80 °C in an oil bath and stirred vigorously for 4 h. After this time, the reaction mixture was cooled to room temperature and then filtered through celite with ether (20 mL). After filtration, the solvents were removed via rotary evaporation. The product was purified by silica gel flash chromatography by eluting with 1% Et_2O in hexanes to give **19a** in 65% yield (73 mg, 0.32 mmol) as a colorless oil, R_f = 0.46 (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, *J* = 10.0 Hz, 2H), 7.11 – 7.09 (m, 4H), 6.83 (d, *J* = 10.0 Hz, 2H), 4.08 (q, *J* = 6.6 Hz, 1H), 3.78 (s, 3H), 2.31 (s, 3H), 1.60 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0, 144.0, 139.0, 135.6, 129.2, 128.7, 127.6, 113.9, 55.5, 43.7, 22.3, 21.2 cm^{-1}. The characterization data matchs with the previously reported data.[30]

4-(1-(4-methoxyphenyl)ethyl)phenol (**19b**):

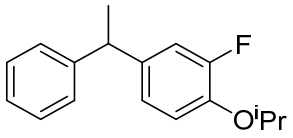


19b

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 83 mg of 4-hydroxyphenyl boronic acid (0.60 mmol, 1.2 equiv), 10 mg of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.01 mmol, 0.02 equiv), 111 mg of 4-methoxyphenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The general procedure for the preparation of **19a** was used to give **19b**. The product was purified by

silica gel flash chromatography by eluting with 10% EtOAc in hexane to give **19b** in 54% yield (61 mg, 0.26 mmol) as yellow oil, R_f = 0.20 (20% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (d, *J* = 10.0, 2H), 7.08 (d, *J* = 5.0 Hz, 2H), 6.83 (d, *J* = 10.0 Hz, 2H), 6.75 (d, *J* = 5.0 Hz, 2H), 4.65 (s, 1H), 4.05 (q, *J* = 6.6 Hz, 1H), 3.78 (s, 3H), 1.58 (d, *J* = 10.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0, 153.8, 139.4, 139.1, 128.8, 128.6, 115.3, 113.9, 55.5, 43.3, 22.5; IR (neat) 3387, 2963, 1609, 1507, 1442, 1239, 1173, 1032, 828, 758, 551 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calcd. for $C_{15}H_{16}O_2Na$: 251.1048 obsd.: 251.1059.

2-fluoro-1-isopropoxy-4-(1-phenylethyl)benzene (**19c**):

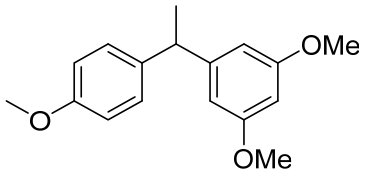


19c

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 119 mg of 3-fluoro-4-isopropoxyphenyl boronic acid (0.60 mmol, 1.2 equiv), 10 mg of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.01 mmol, 0.02 equiv), 98 mg of phenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The general procedure for the preparation of **19a** was used to give **19c**. The product was purified by silica gel flash chromatography by eluting with 10% benzene in hexanes to give **19c** in 40% yield (52 mg, 0.20 mmol) as colorless oil, R_f = 0.36 (20% benzene in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.26 (m, 2H), 7.22– 7.18 (m, 3H), 6.95– 6.86 (m, 3H), 4.47 (sep, *J* = 6.0 Hz, 1H), 4.08 (q, *J* = 8.0 Hz, 1H), 1.61 (d, *J* = 8.0 Hz, 3H), 1.35 (d, *J* = 4.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8 (d, J_{CF} = 244.0 Hz), 146.3, 144.0 (d, J_{CF} = 11.0 Hz), 140.4 (d, J_{CF} = 6.0 Hz), 128.6, 127.7, 126.4, 123.2 (d, J_{CF} = 3.0 Hz), 118.0 (d, J_{CF} = 2.0

Hz), 115.8 (d, J_{CF} = 19.0 Hz), 72.7, 44.1, 22.4, 22.1; IR (neat) 2974, 2931, 1506, 1268, 1123, 955, 915, 870, 771, 698, 644, 591 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calcd. for $C_{17}H_{19}OFNa$: 281.1318 obsd.: 281.1323.

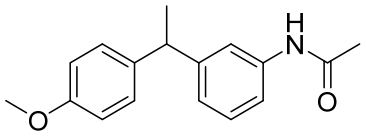
1,3-dimethoxy-5-(1-(4-methoxyphenyl)ethyl)benzene (**19d**):



19d

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 109 mg of 3,5-dimethoxyphenyl boronic acid (0.60 mmol, 1.2 equiv), 10 mg of $Pd_2(dba)_3 \cdot CHCl_3$ (0.01 mmol, 0.02 equiv), 111 mg of 4-methoxyphenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The general procedure for the preparation of **19a** was used to give **19d**. The product was purified by silica gel flash chromatography by eluting with 30% benzene in hexanes to give **19d** in 60% yield (61 mg, 0.26 mmol) as colorless oil, R_f = 0.28 (10% Et_2O in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, *J* = 10.0 Hz, 2H), 6.83 (d, *J* = 5.0 Hz, 2H), 6.38 (d, *J* = 5.0 Hz, 2H), 6.29 (t, *J* = 3.3 Hz, 1H), 4.03 (q, *J* = 6.6 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 6H), 1.59 (d, *J* = 10.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.9, 158.1, 149.5, 138.4, 128.6, 113.9, 106.1, 97.8, 55.4, 44.4, 22.2; IR (neat) 2962, 2361, 1593, 1509, 1456, 1300, 1202, 1148, 828, 694 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$ calcd. for $C_{17}H_{21}O_3$: 273.1491 obsd.: 273.1492.

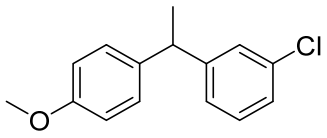
N-(3-(1-(4-methoxyphenyl)ethyl)phenyl)acetamide (**19e**):



19e

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 107 mg of 3-Acetamidobenzene boronic acid (0.60 mmol, 1.2 equiv), 10 mg of $Pd_2(dba)_3 \cdot CHCl_3$ (0.01 mmol, 0.02 equiv), 111 mg of 4-methoxyphenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The general procedure for the preparation of **19a** was used to give **19e**. The product was purified by silica gel flash chromatography by eluting with 30% EtOAc in hexanes to give **19e** in 50% yield (67 mg, 0.25 mmol), R_f = 0.31 (40% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.20 (m, 3H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 4.07 (q, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 2.12 (s, 3H), 1.59 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 158.1, 148.0, 138.4, 138.1, 129.2, 128.7, 123.7, 119.2, 117.8, 114.0, 55.4, 44.1, 24.8, 22.2; IR (neat) 3298, 2966, 2930, 1664, 1609, 1550, 1510, 1487, 1370, 1244, 1178, 1032, 830, 791, 695, 604 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$ calcd. for $C_{17}H_{20}NO_2$: 270.1494 obsd.: 270.1502.

1-chloro-3-(1-(4-methoxyphenyl)ethyl)benzene (**19f**):

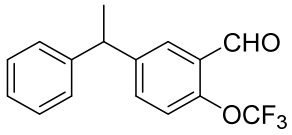


19f

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 94 mg of 3-chlorophenyl boronic acid (0.60 mmol, 1.2 equiv), 10

mg of $Pd_2(dba)_3 \cdot CHCl_3$ (0.01 mmol, 0.02 equiv), 111 mg of 4-methoxyphenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The general procedure for the preparation of **19a** was used to give **19f**. The product was purified by silica gel flash chromatography by eluting with 10% benzene in hexanes to give **19f** in 63% yield (78 mg, 0.32 mmol) as colorless oil, R_f = 0.43 (20% benzene in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 – 7.09 (m, 6H), 6.86 (d, *J* = 10.0 Hz, 2H), 4.10 (q, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 1.62 (d, *J* = 10.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.2, 149.1, 137.8, 134.3, 129.8, 128.7, 127.9, 126.3, 126.0, 114.1, 55.4, 43.9, 22.1 cm^{-1}; The characterization data matchs with the previously reported data.[30]

5-(1-phenylethyl)-2-(trifluoromethoxy)benzaldehyde (**19g**):

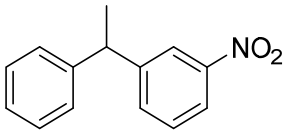


19g

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 140 mg of 3-formyl-4-(trifluoromethoxy)pheny boronic acid (0.60 mmol, 1.2 equiv), 10 mg of $Pd_2(dba)_3 \cdot CHCl_3$ (0.01 mmol, 0.02 equiv), 98 mg of phenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The general procedure for the preparation of **19a** was used to give **19g**. The product was purified by silica gel flash chromatography by eluting with 15% benzene in hexanes to give **19g** in 53% yield (78 mg, 0.27 mmol) as colorless oil, R_f = 0.26 (20% benzene in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.35 (s, 1H), 7.87 (d, *J* = 4.0 Hz, 1H), 7.48 (d, *J* = 4.0 Hz, 1H), 7.33 – 7.19 (m, 6H), 4.22 (q, *J* = 6.6 Hz, 1H), 1.67 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 188.0, 149.4 (q, J_{CF} = 2.1 Hz), 146.2, 145.0, 135.2, 128.9, 128.4, 127.7

(127.69), 127.7 (127.65), 126.8, 121.7 (q, J_{CF} = 1.7 Hz), 120.6 (q, J_{CF} = 259.1 Hz), 44.4, 21.8; IR (neat) 2970, 1696, 1493, 1451, 1250, 1213, 1151, 930, 846, 772, 698, 672 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calcd. for $C_{16}H_{13}O_2F_3Na$: 317.0765 obsd.: 317.0775.

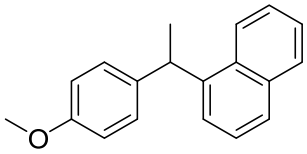
1-nitro-3-(1-phenylethyl)benzene (**19h**):



19h

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 100 mg of 3-nitropheny boronic acid (0.60 mmol, 1.2 equiv), 10 mg of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.01 mmol, 0.02 equiv), 98 mg of phenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The general procedure for the preparation of **19a** was used to give **19h**. The product was purified by silica gel flash chromatography by eluting with 15% benzene in hexanes to give **19h** in 56% yield (64 mg, 0.28 mmol) as yellow oil, R_f = 0.28 (20% benzene in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (t, *J* = 3.3 Hz, 1H), 8.05 (d, *J* = 5.0 Hz, 1H), 7.54 (d, *J* = 10.0 Hz, 1H), 7.44 (t, *J* = 10.0 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.21 (m, 3H), 4.27 (q, *J* = 8.3 Hz, 1H), 1.70 (d, *J* = 10.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.7, 144.9, 134.2, 129.5, 128.9, 127.7, 126.9, 122.6, 121.5, 44.7, 21.8; IR (neat) 2969, 2360, 2341, 1524, 1494, 1344, 1098, 1058, 1028, 895, 806, 734, 700, 669, 580 cm^{-1}; HRMS (ESI) m/z $(M)^+$ calcd. for $C_{14}H_{13}NO_2$: 227.0946 obsd.: 227.0953.

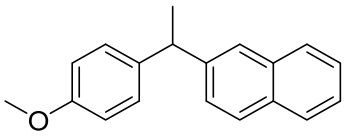
1-(1-(4-methoxyphenyl)ethyl)naphthalene (**19i**):



19i

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 103 mg of 1-naphthyl boronic acid (0.60 mmol, 1.2 equiv), 10 mg of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.01 mmol, 0.02 equiv), 111 mg of 4-methoxyphenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The general procedure for the preparation of **19a** was used to give **19i**. The product was purified by silica gel flash chromatography by eluting with 15% benzene in hexanes to give **19i** in 71% yield (93 mg, 0.35 mmol) as colorless oil, R_f = 0.26 (20% benzene in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (t, *J* = 5.0 Hz, 1H), 7.85 (t, *J* = 2.5 Hz, 1H), 7.74 (d, *J* = 10.0 Hz, 1H), 7.48 – 7.41 (m, 4H), 7.16 (d, *J* = 5.0 Hz, 2H), 6.81 (d, *J* = 10.0 Hz, 2H), 4.89 (q, *J* = 6.6 Hz, 1H), 3.76 (s, 3H), 1.75 (d, *J* = 10.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0, 142.1, 139.0, 134.2, 131.9, 129.0, 128.7, 127.1, 126.0, 125.7, 125.5, 124.4, 124.2, 114.0, 55.4, 39.9, 22.9; IR (neat) 2962, 1609, 1507, 1460, 1300, 1242, 1176, 1030, 829, 798, 726, 557 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calcd. for $C_{19}H_{18}ONa$: 285.1255 obsd.: 285.1257.

2-(1-(4-methoxyphenyl)ethyl)naphthalene (**19j**):

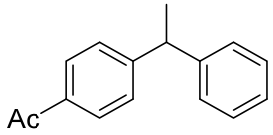


19j

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 103 mg of 2-naphthyl boronic acid (0.60 mmol, 1.2 equiv), 10 mg

of $Pd_2(dba)_3 \cdot CHCl_3$ (0.01 mmol, 0.02 equiv), 111 mg of 4-methoxyphenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The general procedure for the preparation of **19a** was used to give **19j**. The product was purified by silica gel flash chromatography by eluting with 15% benzene in hexanes to give **19j** in 65% yield (85 mg, 0.32 mmol) as colorless oil, R_f = 0.28 (20% benzene in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (t, *J* = 7.5 Hz, 2H), 7.75 (d, *J* = 10.0 Hz, 1H), 7.70 (s, 1H), 7.48 – 7.42 (m, 2H), 7.32 (d, *J* = 10.0 Hz, 1H), 7.20 (d, *J* = 5.0 Hz, 2H), 6.86 (d, *J* = 5.0 Hz, 2H), 4.29 (q, *J* = 6.6 Hz, 1H), 3.79 (s, 3H), 1.73 (d, *J* = 10.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.1, 144.4, 138.6, 133.7, 132.3, 128.9, 128.1, 127.9, 127.8, 127.0, 126.1, 125.5, 125.4, 114.0, 55.4, 44.2, 22.2; IR (neat) 2960, 1608, 1508, 1460, 1301, 1243, 1032, 830, 771, 655 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calcd. for $C_{19}H_{18}ONa$: 285.1255 obsd.: 285.1260.

1-(4-(1-phenylethyl)phenyl)ethan-1-one (**19k**):

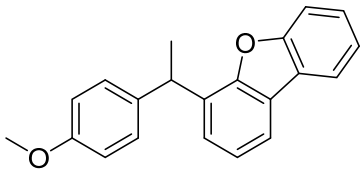


19k

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 73 mg of phenyl boronic acid (0.60 mmol, 1.2 equiv), 10 mg of $Pd_2(dba)_3 \cdot CHCl_3$ (0.01 mmol, 0.02 equiv), 117 mg of 4-acetylphenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The general procedure for the preparation of **19a** was used to give **19k**. The product was purified by silica gel flash chromatography by eluting with 3% EtOAc in hexanes to give **19k** in 48% yield (54 mg, 0.24 mmol), R_f = 0.20 (5% EtOAc in hexanes) as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 5.0 Hz, 2H), 7.32 – 7.28 (m, 4H), 7.22 – 7.19 (m, 3H), 4.21 (q, *J* = 6.7 Hz,

1H), 2.57 (s, 3H), 1.67 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 198.0, 152.2, 145.5, 135.4, 128.8, 128.7, 128.0, 127.8, 126.6, 45.0, 26.8, 21.8 cm^{-1}; The characterization data matchs the previously reported data.[31]

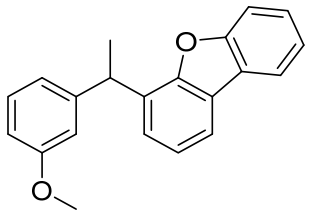
4-(1-(4-methoxyphenyl)ethyl)dibenzo[b,d]furan (**19l**):



19l

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 127 mg of dibenzofuran-4-boronic acid (0.60 mmol, 1.2 equiv), 10 mg of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.01 mmol, 0.02 equiv), 111 mg of 4-methoxyphenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The general procedure for the preparation of **19a** was used to give **19l**. The product was purified by silica gel flash chromatography by eluting with 15% benzene in hexanes to give **19l** in 60% yield (91 mg, 0.30 mmol), R_f = 0.28 (20% benzene in hexanes) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.0 Hz, 1H), 7.82 (dd, *J* = 6.0, 2.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.36 – 7.25 (m, 5H), 6.87 (d, *J* = 12.0 Hz, 2H), 4.83 (q, *J* = 6.6 Hz, 1H), 3.79 (s, 3H), 1.81 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 156.2, 154.3, 137.5, 131.2, 128.8, 127.1, 125.5, 124.8, 124.2, 123.1, 122.8, 120.8, 118.5, 113.9, 111.9, 55.4, 38.3, 21.2; IR (neat) 3360, 2970, 2360, 1609, 1509, 1450, 1302, 1243, 1178, 1090, 1042, 889, 827.5, 749.85, 635 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calcd. for $C_{21}H_{18}O_2Na$: 325.1204 obsd.: 325.1209.

4-(1-(3-methoxyphenyl)ethyl)dibenzo[b,d]furan (**19m**):

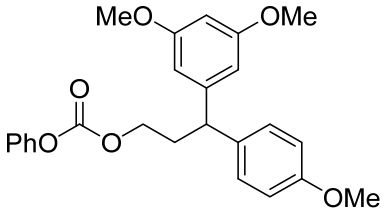


19m

To a 40 mL Schlenk bomb equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 127 mg of dibenzofuran-4-boronic acid (0.60 mmol, 1.2 equiv), 10 mg of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.01 mmol, 0.02 equiv), 111 mg of 3-methoxyphenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 10 mL of ^{t}BuOH. The general procedure for the preparation of **19a** was used to give **19m**. The product was purified by silica gel flash chromatography by eluting with 20% benzene in hexanes to give **19m** in 65% yield (99 mg, 0.33 mmol), R_f = 0.28 (20% benzene in hexanes) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.75 (m, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.31 – 7.17 (m, 4H), 6.96 – 6.93 (m, 2H), 6.72 (dd, *J* = 10.0 Hz, 2.0 Hz, 1H), 4.80 (q, *J* = 6.6 Hz, 1H), 3.74 (s, 3H), 1.78 (d, *J* = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 156.2, 154.3, 147.0, 130.6, 129.5, 127.1, 125.6, 124.8, 124.2, 123.1, 122.8, 120.8, 120.4, 118.7, 114.1, 111.9, 111.4, 55.3, 39.2, 21.0; IR (neat) 2966, 1582, 1449, 1315, 1263, 1182, 1099, 1034, 870, 844, 748, 711 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calcd. for $C_{21}H_{18}O_2Na$: 325.1204 obsd.: 325.1205.

General procedure for 1,1-diarylation of allylic carbonates

3-(3,5-dimethoxyphenyl)-3-(4-methoxyphenyl)propyl phenyl carbonate (**22**):

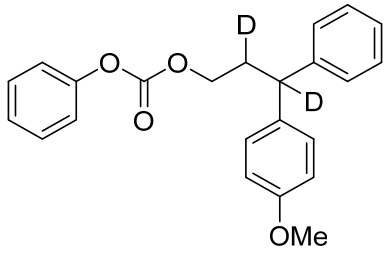


22

To a 20 mL vial equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 109 mg of 3,5-dimethoxyphenyl boronic acid (0.60 mmol, 1.2 equiv), 111 mg of 4-methoxyphenyl diazonium tetrafluoroborate (0.50 mmol, 1.0 equiv), 11 mg of $Pd_2(dba)_3$ (0.013 mmol, 0.025 equiv) and 89 mg of allyl phenyl carbonate (0.50 mmol, 1.0 equiv) in 5.0 mL of THF. The flask was sealed and allowed to stir at room temperature vigorously (rpm > 800) for 2 h. After which, the solvent was removed *in vacuo*. The product was purified by silica gel flash chromatography to give **22** in 84% yield (178 mg) as yellow oil, R_f = 0.2 (30% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.43 (t, *J* = 7.9 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.46 (s, 1H), 6.45 (s, 1H), 6.34 (s, 1H), 4.21 (t, *J* = 6.7 Hz, 2H), 4.03 (t, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 6H), 2.51 – 2.42 (m, 2H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 161.8, 159.1, 154.3, 152.0, 147.5, 136.5, 130.2, 129.3, 126.7, 121.9, 114.7, 106.6, 98.5, 67.9, 56.0, 55.9, 47.5, 34.8; IR (neat): 2936, 2836, 1757, 1592, 1510, 1457, 1241, 1201, 1150, 1052, 829, 687 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calcd. for $C_{25}H_{26}O_6Na$: 445.1627 obsd.: 445.1633.

Deuterium labeling experiment

3-(4-methoxyphenyl)-3-phenylpropyl-2,3-d_2 phenyl carbonate (**24**):

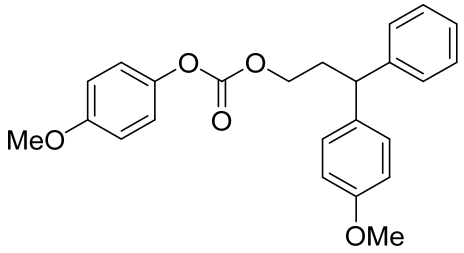


24

The general procedure for the preparation of **22** was used with the modifications that 90 mg of **23** (0.5 mmol, 1.0 equiv), 111 mg of 4-methoxyphenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 73 mg of phenyl boronic acid (0.6 mmol, 1.2 equiv) were used. The product was purified by silica gel flash chromatography to give **24** in 63% yield (115 mg) as colorless oil, R_f = 0.2 (20% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.18 (m, 8H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.22 (d, *J* = 6.6 Hz, 2H), 4.11 (d, *J* = 8.1 Hz, 0.06 H), 3.78 (s, 3H), 2.46 (t, *J* = 6.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 153.8, 151.3, 144.3, 135.9, 129.7, 128.9, 128.8, 127.8, 126.6, 126.2, 121.3, 114.3, 67.3, 55.4, 46.2 (m), 34.1 (m); IR (neat) 1755, 1509, 1236, 1204, 1177, 1022, 774, 697, 686 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calcd.: 387.1541, obsd.: 387.1554.

Cross-over experiment

4-Methoxyphenyl (3-(4-methoxyphenyl)-3-phenylpropyl) carbonate (**25**):



25

To a 20 mL vial equipped with a stir bar, was added 50 mg of $NaHCO_3$ (0.60 mmol, 1.2 equiv), 111 mg of 4-methoxyphenyl diazonium tetrafluoroborate (0.5 mmol, 1.0 equiv) and 73 mg of phenyl boronic acid (0.6 mmol, 1.2 equiv), 11 mg of $Pd_2(dba)_3$ (0.013 mmol, 0.025 equiv), 45 mg of **23** (0.250 mmol, 0.50 equiv) and 52 mg of **25** (0.250 mmol, 0.50 equiv) in 5.0 mL of THF. The flask was sealed and allowed to stir at room temperature vigorously for 2 h. After which, the solvent was removed *in vacuo*. The products were purified via silica gel flash chromatography by eluting with 15% EtOAc in hexanes to give **25** in 40% yield (78 mg, 0.20 mmol) and **24** in 36% yield (66 mg, 0.18 mmol), R_f = 0.2 (20% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 2H), 7.26 – 7.23 (m, 2H), 7.20 – 7.16 (m, 3H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.18 (t, *J* = 6.7 Hz, 2H), 4.08 (t, *J* = 7.9 Hz, 1H), 3.97 (s, 3H), 3.77 (s, 3H), 2.48 – 2.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 157.5, 154.2, 144.9, 144.3, 136.0, 128.9, 128.8, 127.8, 126.6, 122.09, 114.6, 114.2, 67.3, 55.8, 55.4, 46.6, 34.6; IR (neat) 1754, 1505, 1301, 1241, 1199, 1176, 1029, 826, 698 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calcd.: 415.1521 obsd.: 415.1540.

General procedure for the optimization of 1,1-diarylation of ethylene with aryl triflate and aryl boronic acid

To a 40 mL Schlenk bomb equipped with a stir bar, was added 1.2 equiv of base (0.12 mmol, 1.2 equiv), 16 mg of 4-tolyl boronic acid (0.12 mmol, 1.2 equiv), 3 mg of $Pd_2(dba)_3 \cdot CHCl_3$ (0.003 mmol, 0.03 equiv), 27 mg of 4-methylphenyl triflate (0.1 mmol, 1.0 equiv) and 2 mL of DMA. The thick-wall Schlenk bomb was then evacuated followed by pressurization with ethylene at 15 psi at room temperature using a three way adapter. This process was repeated three times and the glass bomb was sealed with Teflon stopcock. The reaction mixture was stirred during the process of evacuation and pressurization. The reaction mixture was then heated to 60 °C in an oil bath and stirred vigorously for 12 h. After this time, the reaction mixture was cooled to room temperature and then filtered through celite with ether (20 mL). After filtration, the solvents were removed via rotary evaporation and analysed by ^{1}H NMR. The modifications described in Table 3.2 were applied in order to optimize the reaction.

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CHAPTER 4

SYNTHESIS OF HIGHLY FUNCTIONALIZED TRI- AND TETRASUBSTITUTED ALKENES VIA PD-CATALYZED 1,2-HYDROVINYLATION OF TERMINAL 1,3-DIENES

Introduction

The development of new chemical transformations for the regio- and stereoselective formation of synthetically useful structures in a rapid and efficient fashion is an important goal for modern synthetic organic chemistry.[1-3] Such transformations would not only save time but also avoid cost by reducing steps, thus making the processes more environmentally friendly and atom-economical. The regio- and stereoselective synthesis of tri- and tetrasubstituted alkenes is one such desired transformation.[4] These alkenes are valuable targets, as they are found in many biologically active molecules[5,6] and natural products.[7-9] Also, these are used as substrates in a variety of organic transformations such as the Sharpless asymmetric epoxidation,[10] dihydroxylation,[11] asymmetric hydrogenation,[12,13] polymerization[14] and materials synthesis.[15] Therefore, it is not surprising that significant effort has been devoted to the stereodefined synthesis of such alkenes over the past few decades.[4]

In the previous chapters, the development of vinylarylation[16] and diarylation[17] of ethylene has been described. These reactions proceed via formation of π-allyl/benzylpalla-

-dium intermediates. In order to expand the versatility of these reactions to different olefin sources as well as nucleophiles, we were interested in developing a method that can couple three different reagents in a single step to generate synthetically useful tri- and tetrasubstituted alkene moieties in a stereodefined fashion.[18]

Background

The most general transition-metal catalyzed method for the formation of multisubstituted alkenes involves the carbometallation of unsaturated molecules, such as alkynes, and allenes to form alkenyl-metal species, which can then be trapped using an electrophile.[4] One of the representative procedures is a Pd-catalyzed three-component reaction, developed by Larock and co-workers, of an internal alkyne **1**, an aryl iodide **2**, and a phenyl boronic acid **3** to form a tetrasubstituted alkene **4** (Figure 4.1a).[19,20] The reaction proceeds via an oxidative addition of Pd(0) to an aryl iodide **2**, followed by *cis*-addition into an alkyne at the less hindered or electron-rich end to form a Pd-alkenyl species **A**, which undergoes cross-coupling with an aryl boronic acid to form **4** in excellent yield. This methodology has also been extended to include a vinyl iodide **6** as an electrophile, which affords highly substituted 1,3-diene **7** in 87% yield (Figure 4.1b).[21]

Another approach involves carbometallation of alkynes with the organometallic reagents, such as organomagnesium, -copper or -zinc reagents to form stereodefined alkenyl-metal species, which can be further transformed to form tri- or tetrasubstituted alkenes. For example, Corey and co-workers reported the synthesis of a trisubstituted alkene **9** by the reaction between α,β-acetylenic ester **8** and Me_2CuLi (Figure 4.2a).[22] Initial carbometallation of an alkyne **8** with an organocuperate is followed by quenching with

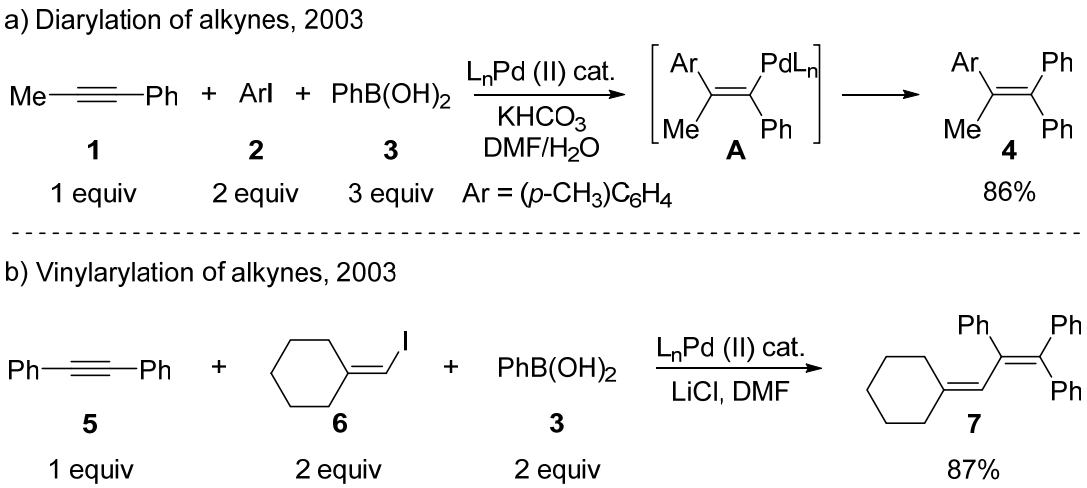


Figure 4.1. Pd-catalyzed difunctionalization of alkynes. a) Pd-catalyzed diarylation of alkynes. b) Pd-catalyzed vinylarylation of alkynes.

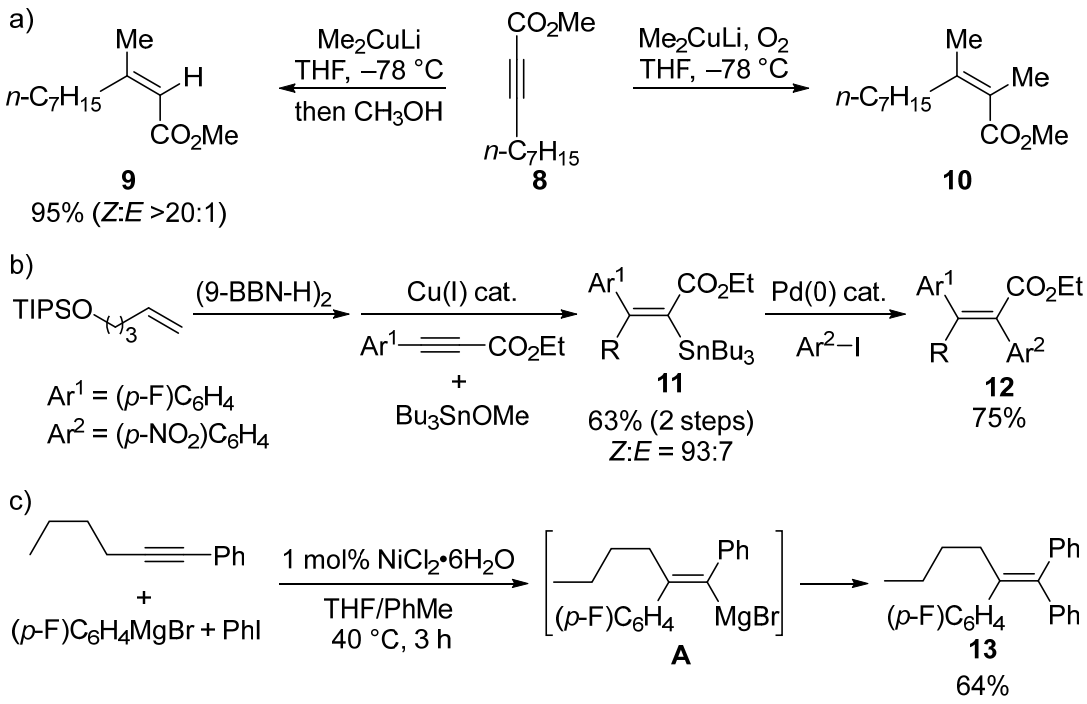


Figure 4.2. Synthesis of tri- and tetrasubstituted alkenes. a) Carbometallation of organocuperate to alkynes from Corey and co-workers, 1969. b) Carbometallation of alkylborane to alkyne followed by stannylation from Sawamura and co-workers, 2013. c) Carbometallation of organomagnesium reagent to alkyne from Hayashi and co-workers, 2015.

methanol at low temperature to form trisubstituted alkene **9** in excellent yield and selectivity. Additionally, it was observed that the use of a large excess of organocuperate reagent in the presence of oxygen[23] gave the tetrasubstituted alkene **10** in an unspecified yield. Recently, Sawamura and co-workers reported a two-step synthesis of a tetrasubstituted alkene **12** (Figure 4.2b).[24] The first step involves the *in situ* generation of an alkyl borane species, which undergoes Cu-catalyzed carbometallation and stannylation of an internal alkyne to form a stereodefined alkenyl stannane **11** in 63% yield and good *cis*-stereoselectivity. Next, **11** undergoes Pd(0)-catalyzed cross-coupling with an aryl iodide to form the tetrasubstituted alkene **12** in 75% yield. In 2015, Hayashi and co-workers reported a one-pot three-component approach involving an alkyne, an aryl Grignard reagent and a phenyl iodide to form the tetrasubstituted alkene **13** in 64% yield (Figure 4.2c).[25] Mechanistically, the first step involves the carbometallation of an alkyne with an aryl Grignard reagent to generate an alkenyl magnesium species **A** *in situ*, which undergoes Ni-catalyzed cross-coupling with the phenyl iodide to afford **13**. In addition to the methods described above, there are numerous other reports of the synthesis of tri- and tetrasubstituted alkenes via initial generation of the stereodefined organometallic species from alkynes.[4] Despite their success, these suffer from several limitations such as the use highly basic organometallic reagents, multistep procedures, low functional group tolerance, and limited scope.

An alternate approach involves the stereodefined synthesis of alkenyl electrophiles, which can be cross-coupled with organometallic reagents to afford tetrasubstituted alkenes with retention of configuration. For example, Brown and co-workers reported the cross-coupling of a stereodefined alkenyl phosphate **15** with benzyl magnesium bromide to form

the tetrasubstituted alkene **16** with slight loss of alkene configuration (Figure 4.3a).[26] The alkenyl phosphate **15** was synthesized from stereoselective addition of an organolithium reagent (*n*-BuLi) to a differentially substituted ketene **B**. This ketene can be obtained from lithium enolate **A**, which was formed from the deprotonation of a hindered ester such as **14** with a strong base. The reaction is limited in scope, as a strong steric bias is required on the ketenes for the stereoselective formation of alkenyl phosphates. Subsequently, Gaunt and co-workers reported a Cu-catalyzed electrophilic carbofunctionalization of a symmetrical alkyne with a hypervalent iodonium salt to from a stereodefined alkenyl triflate **17** in a good yield and selectivity (Figure 4.3b).[27] The reaction proceeds via initial reaction of CuCl with styryl(*o*-tolyl)iodonium salt to form a more reactive Cu(III)-styryl intermediate **C**, which undergoes addition into a symmetrical alkyne to form *Z*-alkenyl Cu species **D**. Subsequently, reductive elimination afforded highly stereoselective alkenyl triflate **17**. This alkenyl triflate **17** can be cross-coupled with an aryl boronic acid to form an all carbon tetrasubstituted alkene **18** in 80% yield without loss of isomeric purity. Recently, Tobrman and co-workers reported a step-wise sequential cross-coupling reaction of an enol phosphate dibromide **19** with three different aryl boronic acids to afford stereodefined tetrasubstituted alkene **20** (Figure 4.3c).[28]

Allenes have been extensively used by Cheng and co-workers for the synthesis of tri- and tetrasubstituted alkenes. In general, the reaction proceeds in a typical fashion, where initial regioselective insertion of a Pd-alkenyl species into the center carbon of an allene forms a π-allylpalladium species **A** similar to that shown in Figure 4.4a. Then, this undergoes cross-coupling with an organometallic reagent to form the stereodefined alkene. In 1999, Cheng and co-workers reported the Pd-catalyzed coupling of a symmetrical allene

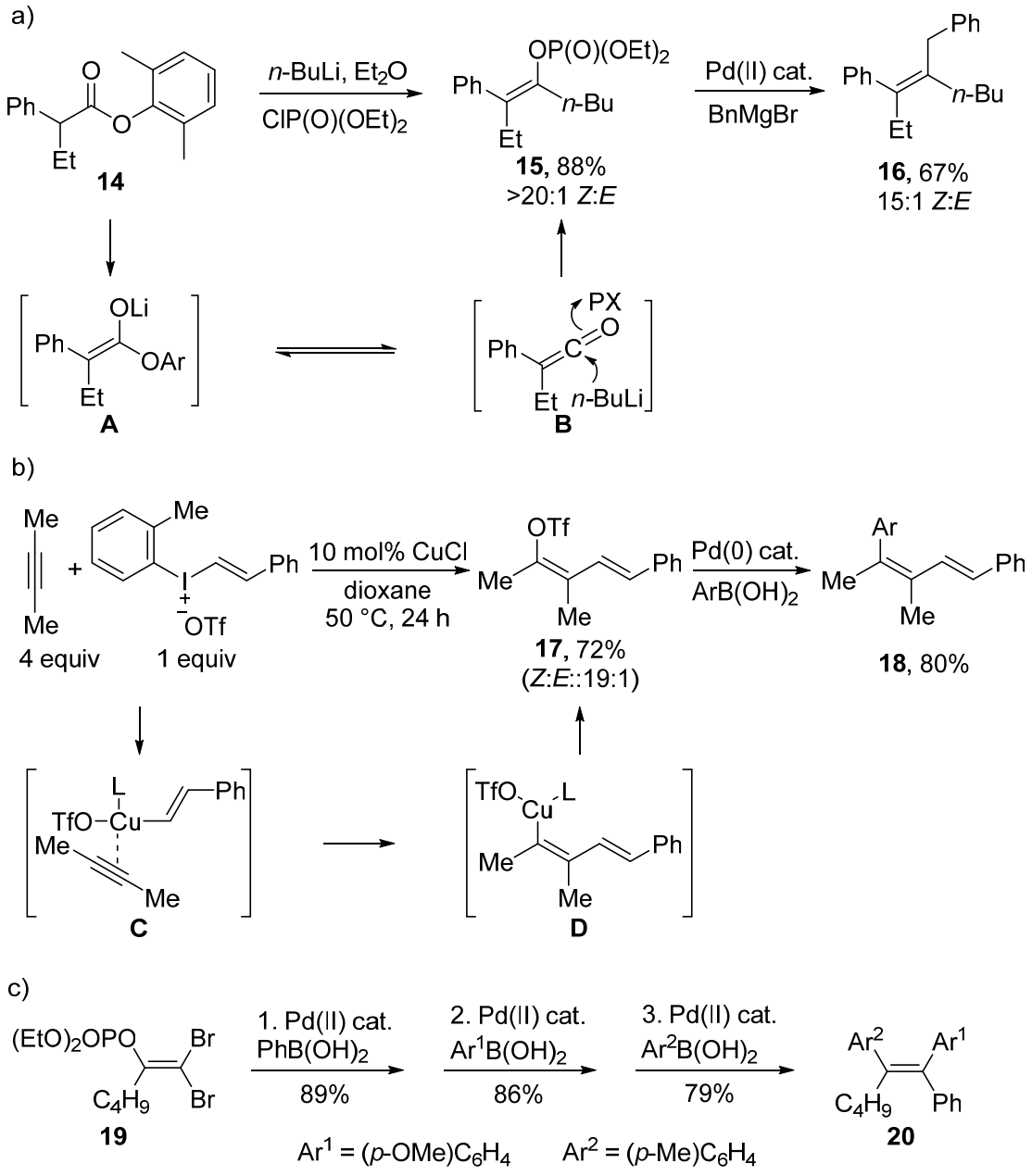


Figure 4.3. Synthesis of tetrasubstituted alkenes via formation of stereodefined electrophiles followed by cross-coupling. a) Synthesis of stereodefined alkenyl phosphate followed by cross-coupling from Brown and co-workers, 2013. b) Synthesis of stereodefined alkenyl triflate followed by cross-coupling from Gaunt and co-workers, 2013. c) Tandem cross-coupling of enol phosphate dibromide from Tobrman and co-workers, 2015.

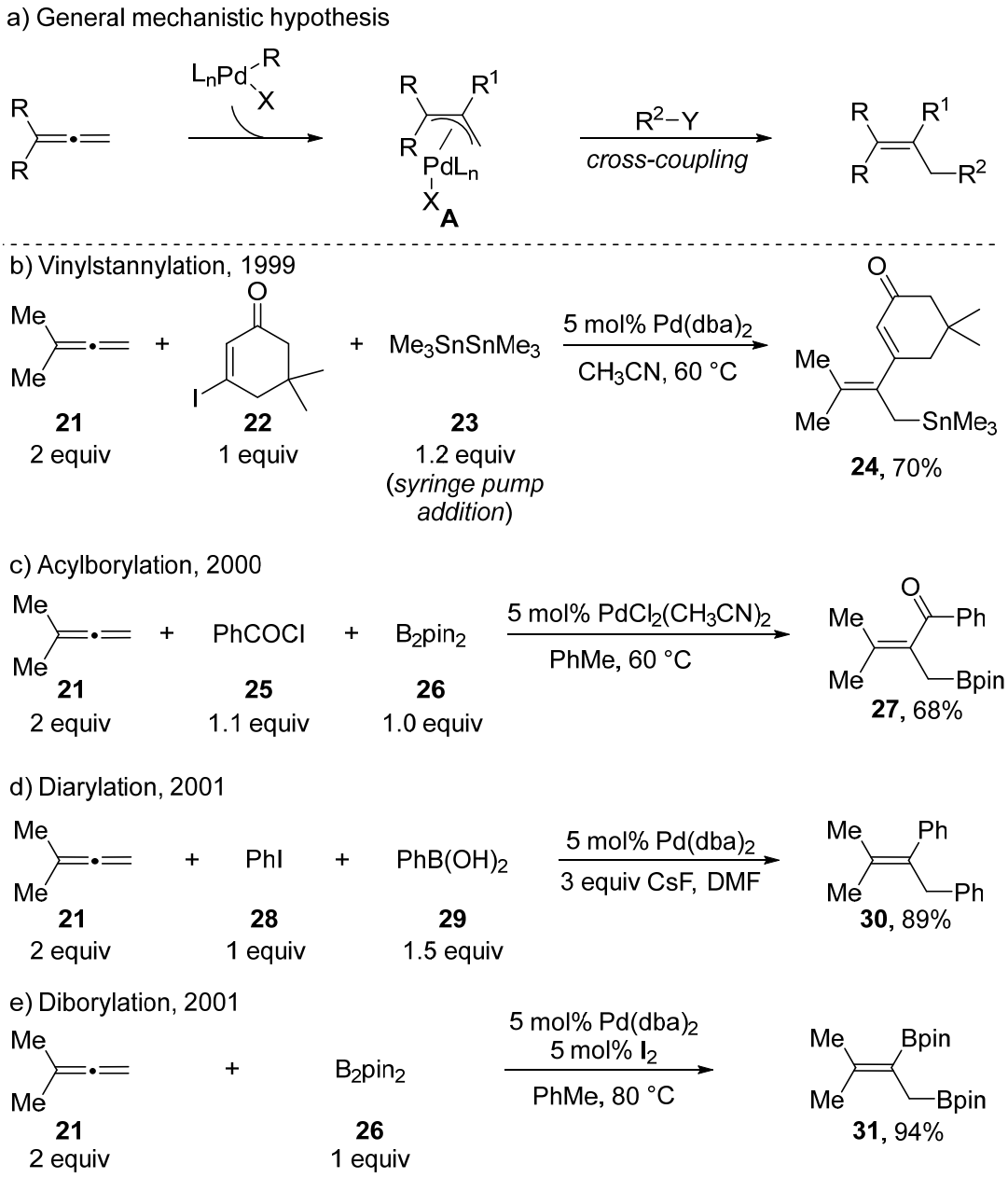


Figure 4.4. Synthesis of tetrasubstituted alkenes from allenes. a) General mechanistic hypothesis. b) Vinylstannylation of allenes. c) Acylborylation of allenes. d) Diarylation of allenes. e) Diborylation of allenes.

21 with a vinyl iodide **22** and hexamethyldistannane **23** to form an allyl stannane **24** in 70% yield (Figure 4.4b).[29] The regioselectivity of the reductive elimination step is favored at a sterically less hindered terminal position. In 2002, a more attractive approach was reported that used an acetyl chloride **25** as an electrophile and bis(pinacolato)diboron **26** as a cross-coupling partner to form a synthetically useful allyl borane **27** in 68% yield. This can be further transformed using cross-coupling, oxidation or nucleophilic addition (Figure 4.4c).[30,31] Soon after, a Pd-catalyzed three-component approach using an allene **21**, an aryl iodide **28** and an aryl boronic acid **29** was reported that afforded the tetrasubstituted alkene **30** in 89% yield (Figure 4.4d).[32] In 2001, the Pd-catalyzed diborylation of allenes was achieved using bis(pinacolato)diboron **26** and catalytic iodine (Figure 4.4e).[33] The key step involved the initial reaction between iodine and a diborane to generate an iodo(pinacolato)boron. This acted as an active electrophile in the reaction and underwent oxidative addition to Pd(0) followed by the general catalytic cycle outlined in Figure 4.4a. Of note here is that stereoselectivity is not an issue in these reactions, since the allene used is symmetrical.

Although significant advancement has been achieved for the expedient, and regio- and stereoselective synthesis of tri- and tetrasubstituted alkenes, these approaches suffer from several limitations. For example, the use of biased alkynes and highly basic organometallic reagents and harsh conditions limit the functional group tolerance as well as scope of the reaction. Also, the generation of tetrasubstituted alkene moieties via cross-coupling reactions is limited to substrates lacking β-hydrogens, which would simplify the system by preventing side products originating from β-hydride elimination. Moreover, multistep procedures limit the synthetic applicability of these reactions. Therefore, we

sought to develop a simple protocol involving a Pd-catalyzed three-component reaction between terminal 1,3-dienes, stereodefined enol triflates and a hydride source, which would lead to the synthesis of tri- and tetrasubstituted alkenes in a single step with retention of configuration.

Results and Discussion

The potential of Pd to catalyze a wide variety of reactions with high levels of chemo-, regio-, and stereoselectivity has been known for decades.[34] Consequentially, a number of multicomponent reactions have been developed by our group[16,17,35,36] and others[1-3] based on palladium catalysis. Recently, our group reported a Pd-catalyzed three-component coupling of terminal 1,3-dienes, alkenyl triflates and aryl boronic acids that led to the formation of 1,2-vinylarylation products in a highly selective manner.[35] Based on a similar approach, a three-component reaction was designed involving terminal 1,3-dienes, stereodefined di- and trisubstituted alkenyl triflates, and a hydride source that would lead to the synthesis of tri- and tetrasubstituted alkenes in a regio- and stereoselective fashion.[18] Mechanistically, the first step involves the oxidative addition of a configurationally defined alkenyl triflate **33** to Pd(0) to form a Pd-alkenyl intermediate **A** (Figure 4.5). The non-coordinating triflate counterion would render the Pd-alkenyl species cationic, which would favor migratory insertion of a 1,3-diene to form a stable π-allylpalladium intermediate **B**. Introduction of a hydride source would allow for the reduction of this intermediate, thus affording the desired product **34** and completing the catalytic cycle. The regioselectivity for the reductive elimination pathway is favored for the 1,2-hydrovinylation product likely due to electronic effects as the resulting disubstituted alkene is in direct conjugation with

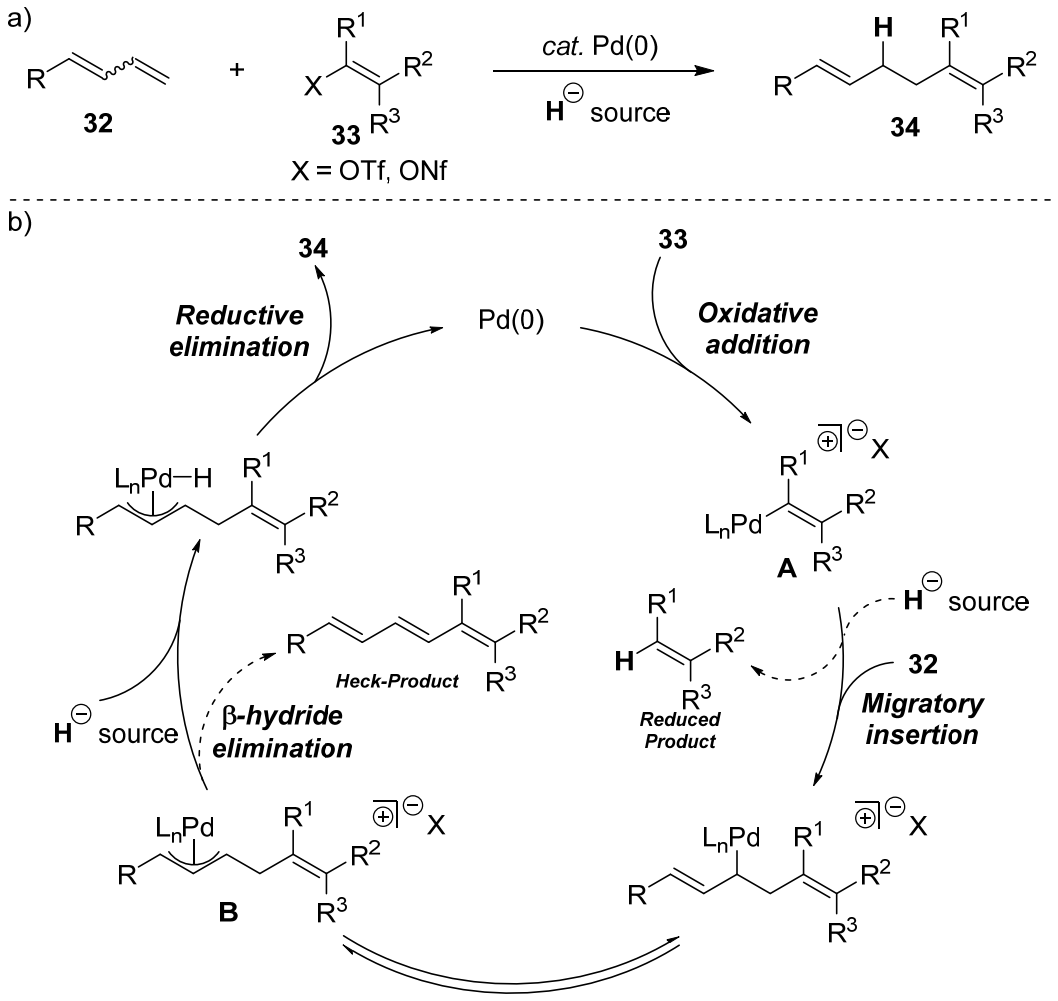


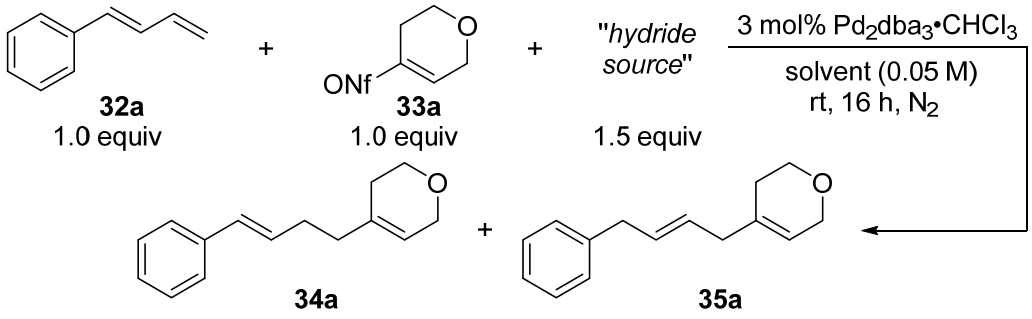
Figure 4.5. Hydrovinylation of terminal 1,3-dienes. a) General reaction. b) Proposed mechanism.

arene. Of note, apart from the direct reduction of Pd-alkenyl species **A**, the possibility of other side reactions cannot be ruled out. For example, the Pd-alkenyl species **A** (in case of an acyclic electrophile) as well as π-allylpalladium intermediate **B** can undergo β-hydride elimination to form an allene and a thermodynamically more stable Heck product, respectively. However, we hypothesize that the electrophilicity of palladium would disfavor such side reactions. For optimization, a simple alkenyl nonaflate **33a** was chosen as an electrophile for reaction with *trans*-1-phenyl-1,3-butadiene **32a** and ammonium

formate. When the reaction mixture was subjected to the conditions previously reported for vinylarylation[35] of dienes, a low yield of hydrovinylation product **34a** was observed (Table 4.1, entry 1). Also, 47% of the unreacted alkenyl nonaflate was observed by ^{1}H NMR. The high conversion of substrate compared to the yield was attributed to the direct reduction of **33a**, although the formation of the reduced side product[37] was not quantified. The screening of various other formate sources revealed sodium formate to be a promising reducing agent as good yield and excellent selectivity was observed (entries 2-4). The use of other hydride sources such as triethylsilane and triethoxysilane were found to be less effective, as low yields and selectivities were observed compared to sodium formate (entries 5,6). The successful use of sodium formate as a reducing agent can be explained by its sparingly soluble nature in DMA, thus maintaining a low concentration in the solution, which would prevent side reactions such as the direct reduction of Pd-alkenyl species **A**, as shown in Figure 4.5. The use of solvents other than DMA, such as THF and *tert*-amyl alcohol, gave poor yields of the desired product (entries 7,8). Concentration of the reaction plays a crucial role, as increasing the concentration of nonaflate from 0.05 M to 0.33 M, significantly enhances the yield (entry 9). The catalyst loading can be reduced to 2 mol% of $Pd_2dba_3 \cdot CHCl_3$, which gave 78% (75% isolated) yield of 1,2-hydrovinylated product in 15:1 regioisomeric ratio (entry 10). Potassium formate gave similar results (entry 11).

After optimization, the scope of the reaction was explored. A range of cyclic alkenyl nonaflates were compatible under the reaction conditions (Figure 4.6). For example, besides dihydropyranyl nonaflate (**34a**), various protected tetrahydropyridine nonaflates gave the corresponding products (**34b**-**34d**) in good to excellent yields and

Table 4.1. Optimization for 1,2-hydrovinylation of terminal 1,3-diene with cyclic nonaflate



entry	solvent	"*hydride source*"	% conv. **33a**[a]	% yield (**34a**/**35a**)[a,b]
1	DMA	HCO_2NH_4	53	5 (nd)
2[c]	DMA	$(HCO_2)_2Zn$	69	52 (15.4:1)
3	DMA	$HCO_2Li•H_2O$	57	46 (16:1)
4	DMA	HCO_2Na	>95	62 (16:1)
5	DMA	Et_3SiH	93	59 (9.6:1)
6	DMA	$(EtO)_3SiH$	84	27 (8.8:1)
7	THF	HCO_2Na	28	4 (nd)
8	*t*-AmOH	HCO_2Na	48	10 (>20:1)
9[d]	DMA	HCO_2Na	>95	79 (15:1)
10[d,e]	DMA	HCO_2Na	>95	78 (15:1)
11[d,e]	DMA	HCO_2K	>95	68 (11:1)

a) Determined by NMR using an internal standard on 0.2 mmol scale. b) Yields are a combination of both **34a** and **35a**. c) Reaction performed with 0.75 equiv of zinc formate. d) Reaction performed in a concentration of 0.33 M in **33a.** e) Reaction performed using 2 mol% $Pd_2dba_3•CHCl_3$. *Note:* For entry 10, reaction performed on 0.5 mmol scale gave 75% yield (both **34a** and **35a**) and 15:1 regioselectivity (**34a**/**35a**).

selectivities. Six membered carbocyclic electrophiles with substitution at the 4-position, such as phenyl (**34e**) and ketal group (**34f**), were coupled efficiently. Furthermore, five- and seven-membered alkenyl nonaflates (**34g**, **34h**) were successfully incorporated. Next, we turned our attention towards utilization of natural product derived vinyl triflates. In particular, the use of vinyl triflates derived from (*1S*)-(−)-camphor (**34i**) and cholesterol (**34j**) gave 81% and 84% yields, respectively. Moreover, the 1,1-disubstituted alkene in

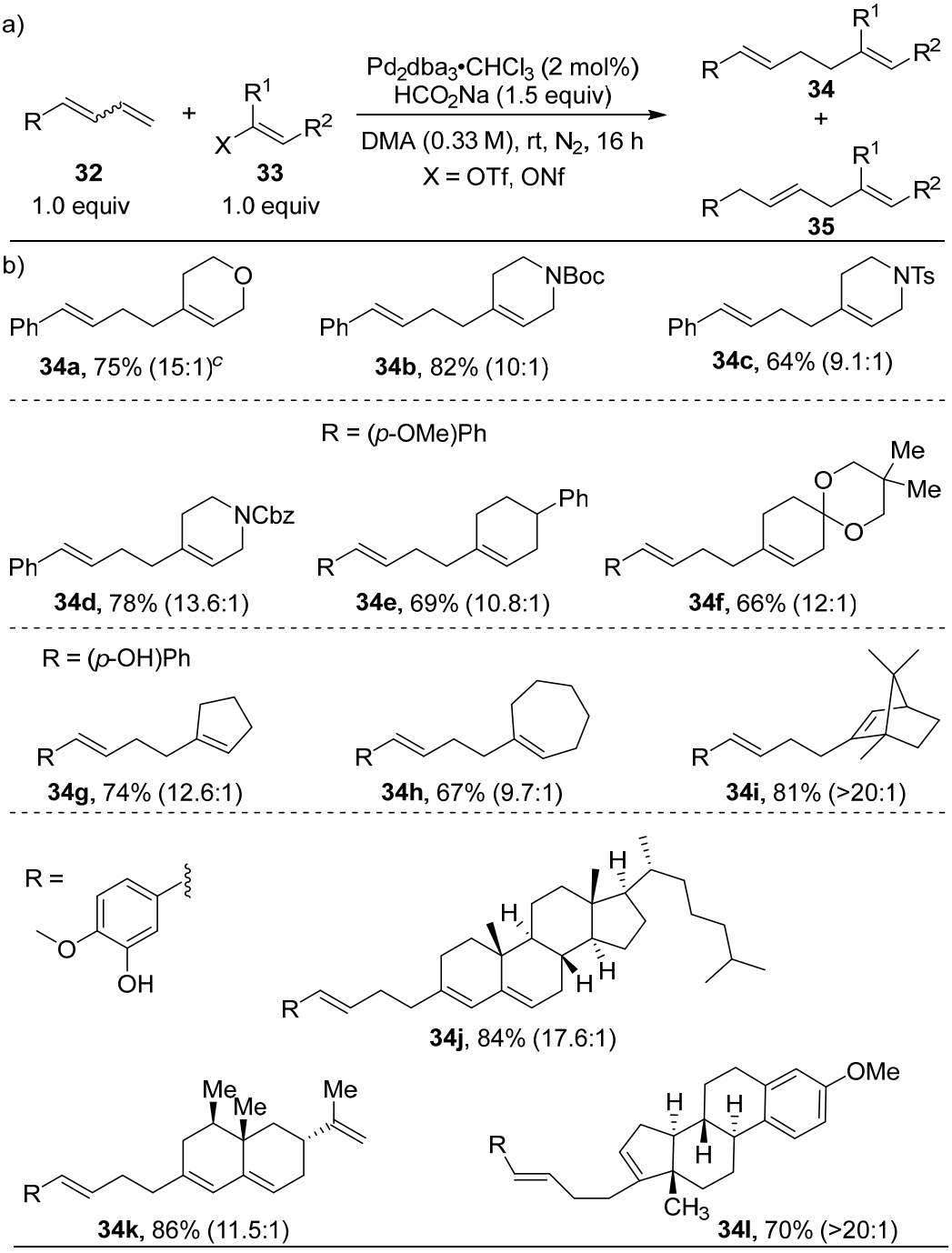


Figure 4.6. Hydrovinylation of terminal 1,3-dienes with cyclic enol triflates/nonaflates. a) General reaction. b) Scope of the reaction. c) The bracket represents the ration of **34**:**35**. All yields are a combination of both **34** and **35**. All yields represents an average of two experiments. *Note*: For **34a-34h** enol nonaflates were used; For **34i-34l**, enol triflates were used.

(+)-nootkatone remained unaltered, and afforded the corresponding product (**34k**) in 86% yield and 11.5:1 regioselectivity. The reaction is insensitive to the steric bias in the triflate, as showcased by the use of an estrone derivative, which gave 70% yield of the desired product (**34l**) in excellent selectivity (>20:1).

To study the origin of regioselectivity, various alkyl substitutions at one end of the diene were explored (Figure 4.7). For example, the use of cyclohexyl-substituted 1,3-diene gave 61% yield of the desired product (**34m**) and >20:1 selectivity in favor of 1,2-hydrovinylation product. However, modest selectivity (5.4:1) was observed when 4,4-dimethyl-1-vinylcyclohexene (**34n**) was used under the reaction conditions. The origin of selectivity can be attributed to the formation of the thermodynamically more stable endocyclic alkene product. Although the geraniol derived diene gave lower regioselectivity (**34o**), in general, the selectivity can also be switched for the formation of 1,2-hydrovinylation product using steric effect of alkyl substituents.

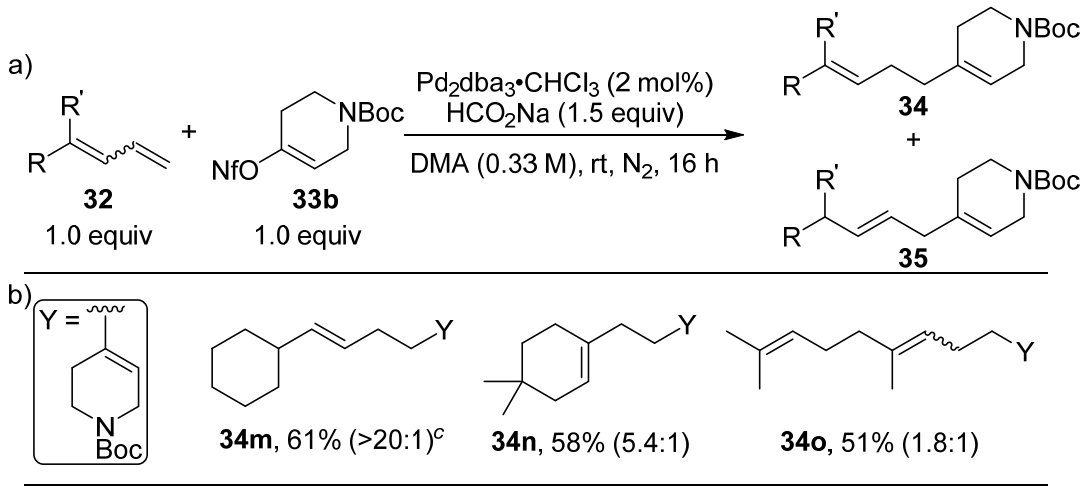
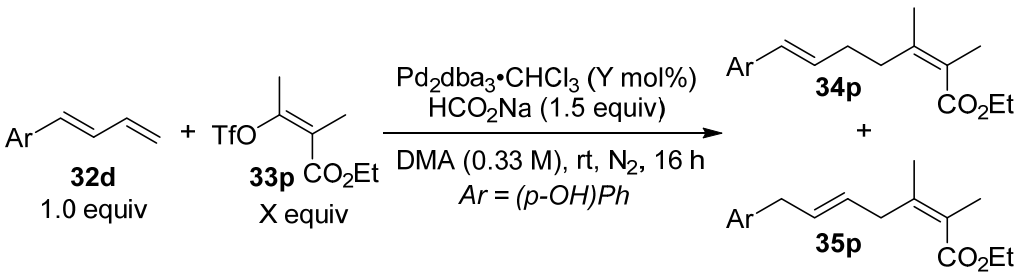


Figure 4.7. Hydrovinylation of alkyl substituted terminal 1,3-dienes with cyclic alkenyl nonaflate. a) General reaction. b) Scope of the reaction. c) The bracket represents the ratios of **34**:**35**. All yields are a combination of both **34** and **35**. All yields represents an average of two experiments.

Next, we turned our attention towards the coupling of synthetically more diverse acyclic (*E*)- and (*Z*)-alkenyl triflates to give tri- and tetrasubstituted alkenes with retention of configuration. A typical procedure for the synthesis of acyclic (*E*)- and (*Z*)-alkenyl triflates involves the reaction of a metal-enolate with a triflating agent such as triflic anhydride or *N*-phenyl-bis(trifluoromethanesulfonimide), where the stereoselectivity depends on the choice of solvent.[38] Recently, Frantz and co-workers reported a practical approach that allowed access to stereodefined di- and trisubstituted alkenyl triflates, starting from cheap and easily accessible β-ketoesters.[39] Although, the synthesis of configurationally defined alkenyl triflates is well-precedented, their use in the formation of stereodefined olefins is limited. This can be attributed to the inherent instability associated with these electrophiles. For example, these electrophiles undergo elimination-isomerization reactions in the presence of a base and under Pd-catalysis.[40] In fact, this property has been exploited by Frantz and co-workers for the synthesis of a variety of useful compounds; such as dienes,[40] heteroaromatics,[41] and chiral allenes.[42] Additionally, base-mediated elimination of acyclic alkenyl triflates is an established protocol for the synthesis of alkynyl esters.[43] Therefore, we were initially concerned with the reactivity of these triflates. However, the mild reaction conditions employed in our system allowed for successful coupling of (*Z*)-alkenyl triflate **33p** to afford (*Z*)-tetrasubstituted alkene **34p** in 45% yield (Table 4.2, entry 1). Further optimization such as increase in the stoichiometry of the alkenyl triflate and catalyst loading afforded 68% yield and 17:1 regioselectivity in favor of 1,2-hydrovinylated product (entries 2,3). Of note was that no deterioration of the initial alkene stereochemistry was observed by ^{1}H NMR.

The reaction can be scaled up to 7.0 mmol in a highly concentrated reaction mixture

Table 4.2. Optimization for 1,2-hydrovinylation of terminal 1,3-diene with acyclic alkenyl triflate



entry	X	Y	% conv. **32d**	% yield (**34p/35p**)[a]
1	1.0	2	80	45 (>20:1)
2	1.3	2	83	55 (>20:1)
3	1.3	5	95	68 (17:1)

a) Determined by NMR using an internal standard on 0.2 mmol scale. Yields are a combination of both **34p** and **35p**.

of 1.0 M in diene, which afforded the compound **34p**' in an isolated yield of 1.6 g (Figure 4.8). Installation of various other triflates, containing functional groups such as *N*-phthalimide protected amine (**34q**) and an alkyl silane (**34r**) at the *β*-position afforded hydrovinylation products in good yields. Substitution at the *α*-position, with, for example, a benzyl group (**34s**) and an alkyl silane (**34t**), is also compatible, albeit with lower yields. An alkenyl triflate bearing a lactone (**34u**) reacted smoothly to give 58% yield of the product. Unfortunately, the use of an (*E*)-alkenyl triflate under the reaction conditions afforded 6.6:1 mixture of (*E*)- and (*Z*)-tetrasubstituted alkene, although only one regioisomer was observed (Figure 4.9). However, the reaction of (*E*)-hydroxymethylene triflate, obtained by reduction of the corresponding ester with DIBAL-H,[44] yielded (*E*)-alkene (**34w**) without any loss of stereochemical integrity as observed by ^{1}H NMR. In fact, (*Z*)-hyroxymethylene triflate can be coupled in a similar fashion to yield **34x** in 67% yield. Conversely, (*E*)-disubstituted triflates reacted efficiently to afford (*E*)-trisubstituted

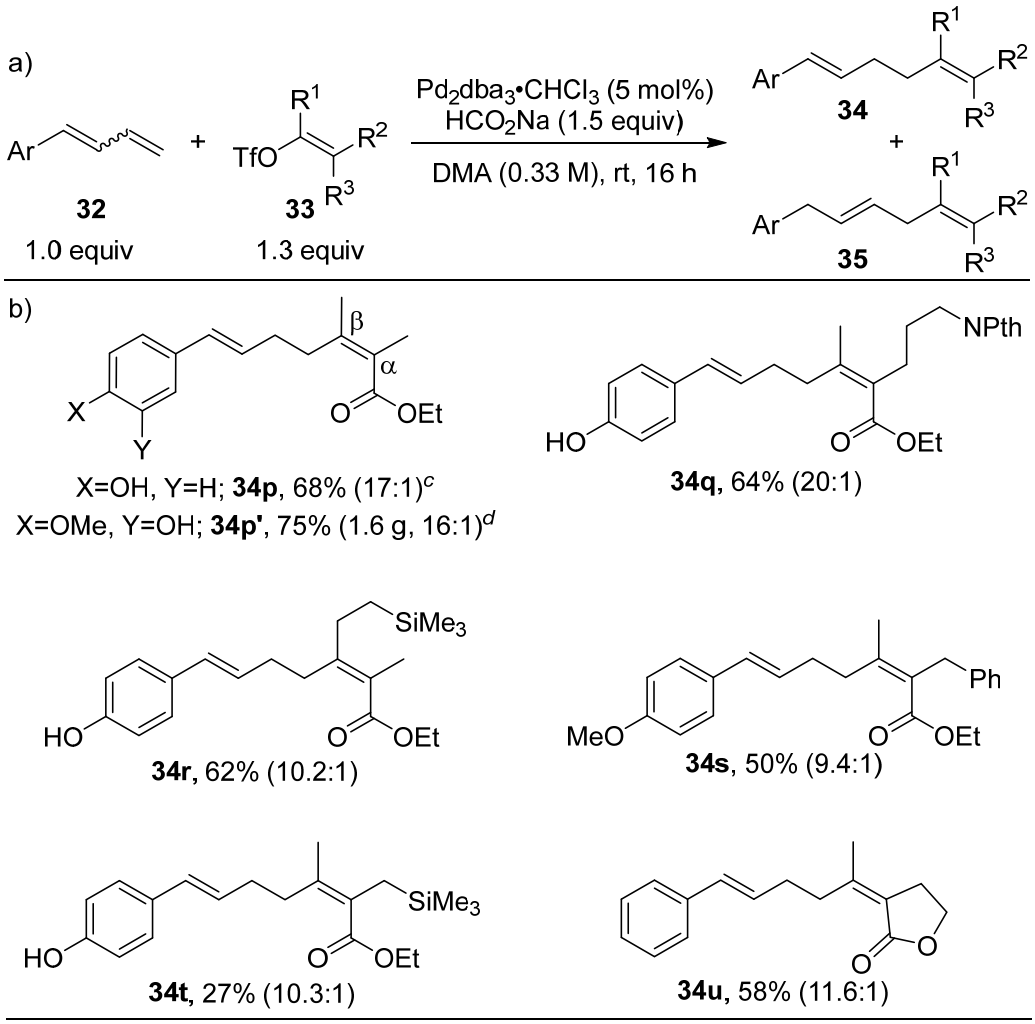


Figure 4.8. Hydrovinylation of terminal 1,3-dienes with (*Z*)-alkenyl triflates. a) General reaction. b) Scope of the reaction. c) The bracket represents the ratios of **34**:**35**. All yields are a combination of both **34** and **35**. All yields represent an average of two experiments. d) The reaction was performed on 7.0 mmol scale and 1.0 M conc. of diene.

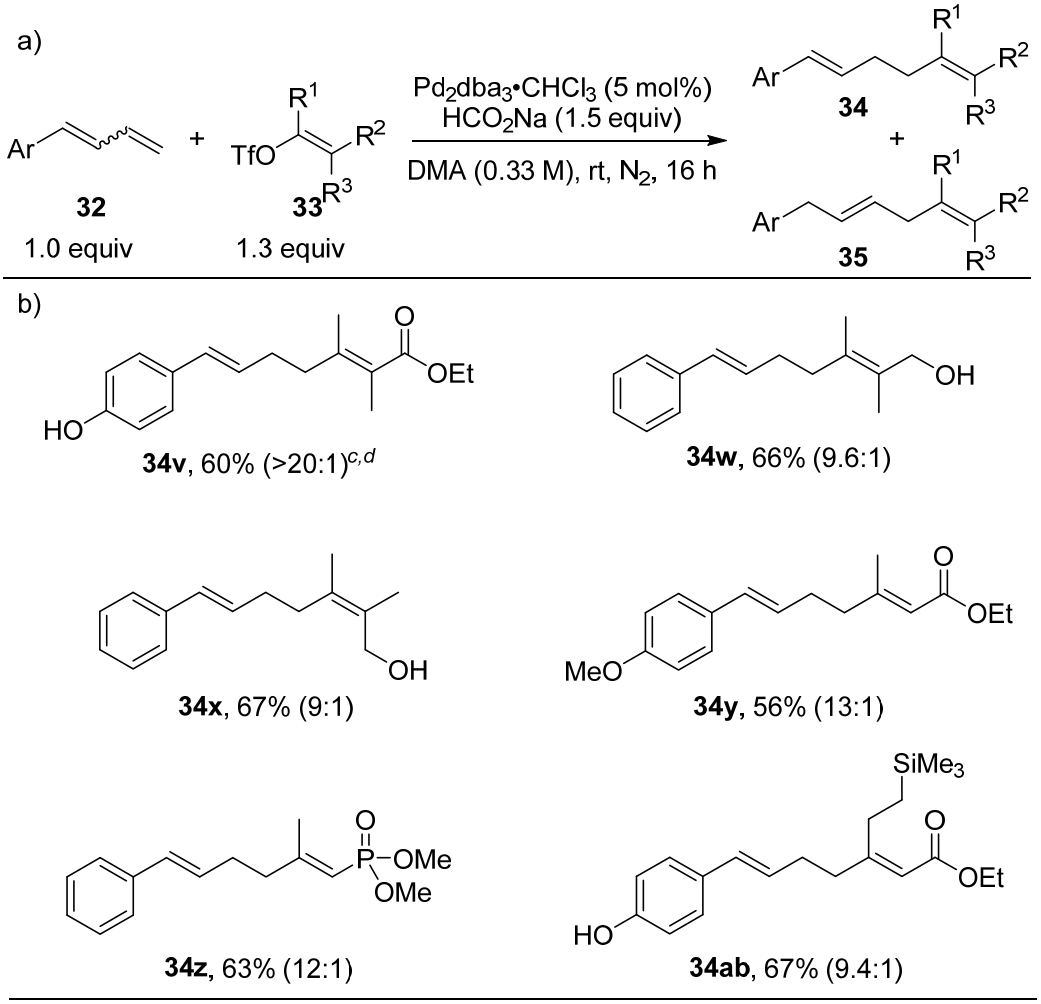


Figure 4.9. Hydrovinylation of terminal 1,3-dienes with (*E*)- and (*Z*)- alkenyl triflates. a) General reaction. b) Scope of the reaction. c) The bracket represents the ratios of **34**:**35**. All yields are a combination of both **34** and **35**. All yields represent an average of two experiments. d) Mixture of (*E*) and (*Z*) isomers were observed (**34v**:**34p**::6.6:1).

alkenes, as shown in the successful synthesis of **34y**-**34ab**.

Finally, the disubstituted alkene present in **34p'** can be selectively reduced in the presence of the electron-deficient tetrasubstituted alkene using hydrogen and catalytic Pd/C to afford **36** in a quantitative yield (Figure 4.10). Thus, the methodology can also be considered as a two-step alkylation of stereodefined trisubstituted alkenyl triflates.

Future Directions

A portion of our group's research is focused on the enantioselective Heck reaction of a wide variety of stereodefined alkenes.[45-48] For example, a recent report showcased the Pd(II)-catalyzed Heck reaction between an aryl boronic acid and a stereodefined trisubstituted alkenol to form a compound bearing a quaternary center (**37**) in excellent yield and enantioselectivity (Figure 4.11a).[47] Next, we wanted to use the route described in this chapter to access stereodefined tetrasubstituted alkenes as substrates in the enantioselective Heck reaction, which would lead to compounds containing vicinal chiral centers.

Alkene substrate **38**, obtained from **36** via reduction, was submitted to the conditions previously optimized for Heck-arylation of trisubstituted alkenols,[47] and led to

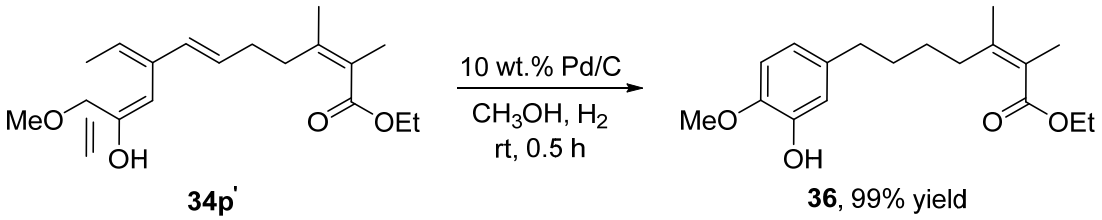


Figure 4.10. Selective reduction of a disubstituted alkene in the presence of a tetrasubstituted alkene.

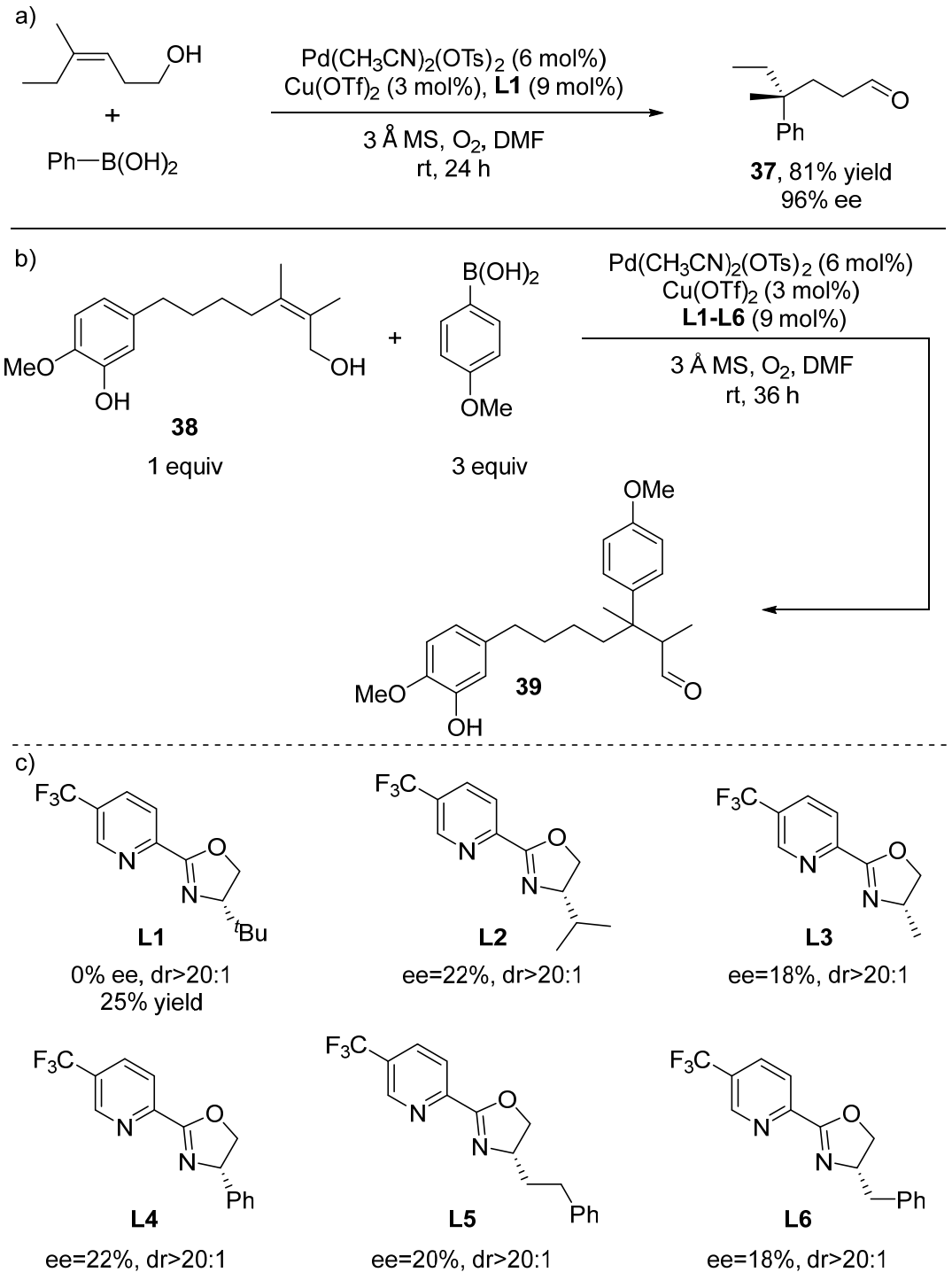


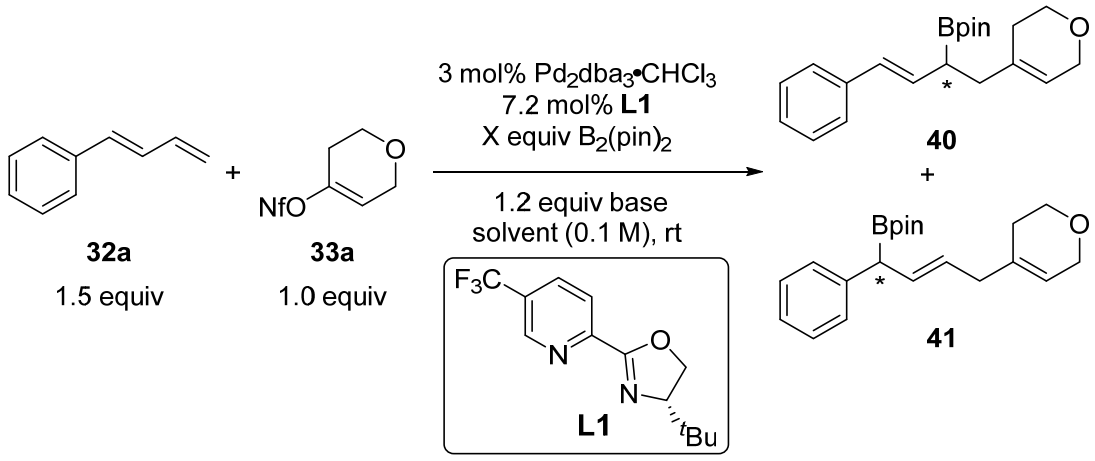
Figure 4.11. Enantioselective Heck reaction. a) Use of trisubstituted alkenols as described by Sigman and coworkers in 2014. b) Use of tetrasubstituted alkenols. c) Results of different ligand screens.

25% yield of **39** with >20:1 diastereoselectivity, albeit no enantioselectivity was observed. Our hypothesis was that the bulky *tert*-butyl group present on the oxazoline ring of the ligand **L1**, is interacting with the alkene substrate, leading to the ligand dissociation from the palladium before migratory insertion. As a result, a variety of different ligands bearing less hindered groups on the oxazoline ring were used under the reaction conditions, as shown in Figure 4.11b. Excitingly, 22% and 18% ees were observed with ligands containing isopropyl (**L2**) and methyl (**L3**) groups, respectively. This suggests that our hypothesis that sterically less demanding groups are required to prevent poor interactions between the catalyst and the substrate, which would increase the chances of rendering this reaction enantioselective. Currently, this project is in the initial stages of optimization, and we are planning to extend the ligand screen to a variety of other pyrox as well as quinox ligand class.

As discussed in Chapter 1, we are also interested in applying π-allyl/benzyl palladium formation approach for stabilizing Pd-alkyl species, which can be further transformed to complex and challenging structural motifs. The use of cheap feedstock olefins has made this strategy synthetically more attractive. Therefore, after successful completion of 1,2-hydrovinylation of terminal 1,3-dienes to form stereoselective alkenes,[18] we wanted to further extend this three-component strategy to generate more complex molecules by employing different nucleophiles instead of sodium formate. Since allyl boranes[49] are important motifs in organic chemistry, which serve as building blocks for a variety of structurally complex and useful compounds, we wanted to use bis(pinacolato)diboron under the reaction conditions instead of sodium formate. For initial investigation, diene (**32a**), nonaflate (**33a**) and bis(pinacolato)diboron were combined to

react under the conditions previously optimized for 1,2-hydrovinylation of dienes.[18] Excitingly, 44% yield of vinylborylated products (**40** and **41**) was isolated in 2.9:1 regioselectivity and 84% ee (Table 4.3, entry 1). Further analysis and time course of the reaction revealed that the desired vinylborylated products are decomposing to hydrovinylation products, presumably via Pd-catalyzed protodeborylation or direct reaction with proton (entries 1-3 and Figure 4.12). Therefore, for further optimization, the reaction was performed for 5 h to avoid *in situ* degradation of products. Increasing the amount of bis(pinacolato)diboron led to excellent yield of the mixture of vinylborylated

Table 4.3. Optimization for the Pd(0)-catalyzed 1,2-vinylborylation of terminal 1,3-diene



entry	solvent	base	X	time (h)	yield (**40**+**41**)	ratio (**40**:**41**)	er
1	DMA	Na_2CO_3	1.5	16	44	2.9:1	92:8
2	DMA	Na_2CO_3	1.5	8	50	1.8:1	92:8
3	DMA	Na_2CO_3	1.5	4.5	31	1.5:1	91:9
4	DMA	Na_2CO_3	3.0	5	88	2.1:1	92:8
5	EtOAc	Na_2CO_3	3.0	5	88	1:1	87:13
6	EtOH	Na_2CO_3	3.0	5	64	1.7:1	88:12
7	DMA	K_2CO_3	3.0	5	53	8.6:1	90:10

Note: Yields determined by GC using 2-methylnapthalene as internal standard.

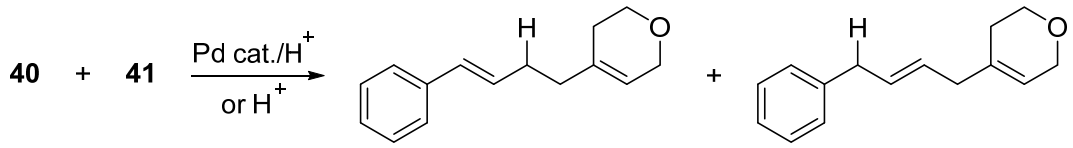


Figure 4.12. Proposed decomposition of vinylborylation products to hydrovinylation products.

products, albeit low regioselectivity was observed (entry 4). Other solvents such as EtOAc and EtOH also gave promising yields (entries 5,6). The use of potassium carbonate as a base instead of sodium carbonate gave excellent regioselectivity in favor of 1,2-vinylborylated product (entry 7). Next, we turned our attention towards studying the effect of different ligands on enantioselectivity of the reaction, as shown in Figure 4.13. The use of sterically less hindered substituents such as isopropyl, methyl, phenyl, and benzyl groups on the oxazoline portion of the ligands (**L2**-**L5**) gave low enantioselectivities. The use of ligand containing no substitution on the pyridine ring of the ligand (**L6**) gave lower ee than the use of ligand **L1**. This shows electron deficient groups on the 5-position of pyridine ring are crucial for higher ee. Use of both electron-rich and electron-poor groups at the 4-position of pyridine ring of ligands (**L7**, **L8**) gave better ee than the ligand with no substitution (**L6**). A nitrile bearing ligand (**L9**) gave only 25% ee of the product, likely due to the nitrile group acting as a ligand for palladium and it can be considered as an outlier. Substitution at the 6-position on the pyridine ring (**L10**-**L12**) lowers the enantioselectivity. Changing to a different ligand class, such as quinoline-oxazoline ligand **L13**, gave only 2% ee. The next ligand design would be the use of more hindered group than *tert*-butyl group on the oxazoline portion of the pyrox ligand.

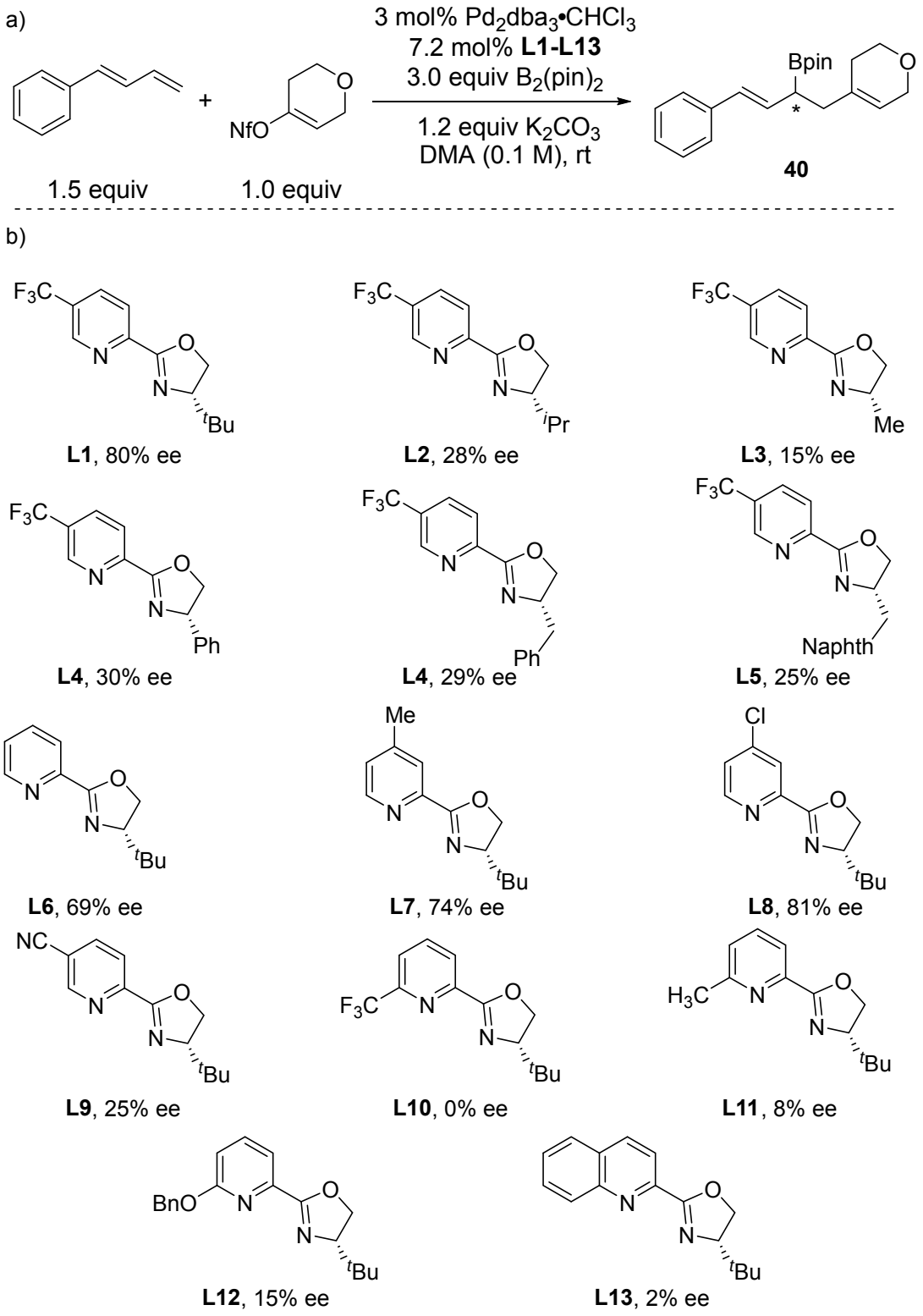


Figure 4.13. Screening of various ligands to determine their effect on enantioselectivity of 1,2-vinylborylation reaction of terminal 1,3-dienes. a) General reaction. b) Results of different ligand screens.

Conclusion

In conclusion, we have disclosed a Pd(0)-catalyzed three-component approach for the efficient construction of Csp^2–Csp^3 bonds in a regio- and stereoselective fashion involving 1,3-terminal dienes, alkenyl triflates/nonaflates, and sodium formate. The mechanism is proposed to proceed via formation of a π-allylpalladium species, which is trapped by a hydride source to form structurally complex and synthetically challenging tri- and tetrasubstituted alkenes. Future directions are directed towards the use of these stereodefined alkenes as building blocks for application in the relay Heck reactions under study in our lab. We are also planning to extend the three-component difunctionalizationreactions of dienes to other nucleophiles such as bis(pinacolato)diboron, which would yield structurally complex and synthetically useful 1,2-vinylborylation products in a regio- and enantioselective fashion.

Experimental

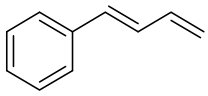
General considerations

Anhydrous *N,N*-dimethylacetamide (DMA) was purchased from Sigma-Aldrich and dried over activated 3 Å molecular sieves. THF was passed through an alumina column (Innovative Technology®) solvent system. Anhydrous ^{t}AmOH was used as purchased from Sigma-Aldrich. Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct was prepared according to the reported procedure.[50] Cyclic enol nonaflates and triflates were prepared according to the literature procedures.[51,52] Acyclic enol triflates were prepared according to the literature procedures unless otherwise mentioned.[39,53] All other reagents were obtained from commercial sources and used without further purification. ^{1}H NMR

spectra were obtained at 300 MHz, 400 MHz or 500 MHz, chemical shifts are reported in ppm, and referenced to the $CDCl_3$ singlet at 7.26 ppm or the CD_2Cl_2 singlet at 5.32 ppm. ^{13}C NMR spectra were obtained at 75 MHz, 100 MHz or 126 MHz and referenced to the center line of the $CDCl_3$ triplet at 77.23 ppm or the CD_2Cl_2 quintet at 53.84 ppm. The abbreviations s, d, t, q, quint, sex, sep, dd, dt, td, m and br stand for the resonance multiplicities singlet, doublet, triplet, quartet, quintet, sextet, septet, doublet of doublets, doublet of triplets, triplet of doublets, multiplet and broad signal, respectively. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with solvents indicated, visualized by a 254 nm UV lamp and stained with phosphomolybdic acid stain. Flash chromatography was performed using EM reagent silica 60 (230-400 mesh). IR spectra were recorded using a Thermo Nicolet FT-IR. High resolution mass spectrometry (HRMS) data were obtained on a Waters LCP Premier XE instrument by ESI/TOF. *Note:* The ^1H NMR and ^{13}C NMR spectra of unknown compounds can be obtained through Marriot Library.

Preparation of starting materials

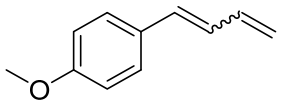
(*E*)-buta-1,3-dien-1-ylbenzene (**32a**):



32a

Prepared according to the literature procedure.[54] Analytical data matchs the literature.[54]

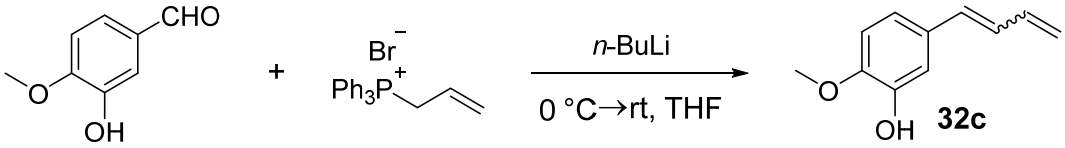
1-(buta-1,3-dien-1-yl)-4-methoxybenzene (**32b**):



32b

Prepared according to the literature procedure.[55] Analytical data matchs the literature.[55]

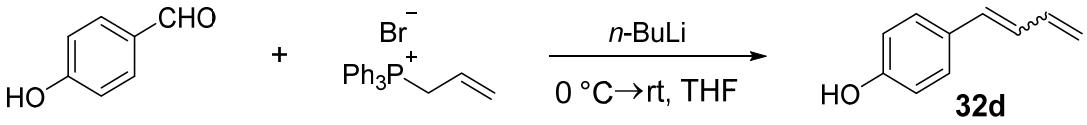
5-(buta-1,3-dien-1-yl)-2-methoxyphenol (**32c**):



To a 250 mL oven dried round bottom flask, was added 9.6 g of allyltriphenylphosphonium bromide (2.5 equiv, 25 mmol). The flask was purged with N_2 and 100 mL of THF was added. The suspension was cooled to 0 ºC and 9.2 mL of a *n*-BuLi solution (2.5 M solution in hexanes, 23 mmol, 2.3 equiv) was added dropwise by syringe. The reaction mixture was stirred for 15 min followed by a dropwise addition of 1.5 g of isovanillin (1.0 equiv, 10 mmol) dissolved in 15 mL of THF. After 1 h, the reaction mixture was allowed to slowly warm to room temperature and stirred for 16 h. A saturated solution of NH_4Cl (50 ml) was added followed by extraction with Et_2O (2x50 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and solvents were removed under reduced pressure. The product was then purified by flash column chromatography (10→20% Et_2O:hexanes) to afford **32c** as a white solid (1.4 g, 80% yield, *Z*:*E*::2.4:1.0), Mp = 32 ºC, R_f = 0.13 (5% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) reported as a mixture of isomers relative to 1H of *Z* isomer; δ 7.04 (d, *J* = 5.0 Hz, 0.38H), 6.95-6.87 (m, 2.24H), 6.82 (d, *J* = 1.5 Hz, 2H), 6.80 (d, *J* = 5.0 Hz, 0.40H), 6.66 (dd, *J* =

17.5, 12.5, 0.42H), 6.51-6.44 (m, 0.78H), 6.35 (d, *J* = 10.0 Hz, 1H), 6.18 (t, *J* = 10.0 Hz, 1H), 5.58 (s, 1H), 5.57 (s, 0.29H), 5.35 (d, *J* = 15.0 Hz, 1H), 5.29 (d, *J* = 15.0 Hz, 0.42H), 5.20 (d, *J* = 10.0 Hz, 1H), 5.12 (d, *J* = 10.0 Hz, 0.39H), 3.39 (s, 3H), 3.89 (s, 1.08H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 146.0, 145.8, 145.4, 137.4, 133.5, 132.6, 131.1, 130.1, 129.9, 128.3, 121.4, 119.3, 119.2, 116.9, 115.3, 112.0, 110.8, 110.6, 56.1; ATR-FTIR (neat); 3510, 3010, 2935, 2839, 2360, 2342, 1575, 1506, 1439, 1264, 1227, 1210, 1128, 1025, 1002, 966, 905, 817, 762, 668 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{11}H_{13}O_2$: 177.0916 observed: 177.0915.

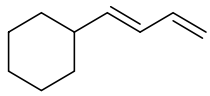
4-(buta-1,3-dien-1-yl)phenol (**32d**):



The same general procedure as that for the synthesis of **32c** was followed using 1.2 g of *para*hydroxybenzaldehyde (10 mmol, 1.0 equiv), 9.6 g of allyltriphenylphosphonium bromide (25 mmol, 2.5 equiv) and 9.2 mL of a *n*-BuLi solution (2.5 M solution in hexanes, 23 mmol, 2.3 equiv). The product was then purified by flash column chromatography (10→20% Et_2O:hexanes) to afford **32d** as a yellow paste (1.40 g, 96% yield, *Z*:*E*::1.5:1.0), R_f = 0.33 (20% Et_2O:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) reported as a mixture of isomers relative to 1H of *Z* isomer; δ 7.31 (d, *J* = 5.0 Hz, 1.20H), 7.23 (d, *J* = 10.0 Hz, 2H), 6.92-6.85 (m, 1H), 6.82 (d, *J* = 10.0 Hz, 2H), 6.80 (d, *J* = 10.0 Hz, 1.18H), 6.67 (dd, *J* = 15.0, 10.0 Hz, 0.74H), 6.50 (dt, *J* = 20.0, 7.5 Hz, 1.25H), 6.39 (d, *J* = 10.0 Hz, 1H), 6.20 (t, *J* = 10.0 Hz, 1H), 5.36 (d, *J* = 20.0 Hz, 1H), 5.30 (d, *J* =15.0 Hz, 0.65H), 5.21 (d, *J* = 10.0 Hz, 1H), 5.13 (d, *J* = 10.0 Hz, 0.67H), 5.08 (s, 0.58H), 5.07 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3, 154.7, 137.5, 133.4, 132.5, 130.7, 130.5, 130.4, 130.0, 129.7, 128.1,

128.0, 119.3, 116.8, 115.8, 115.4; ATR-FTIR (neat); 3350, 2989, 2870, 2360, 1608, 1509, 1445, 1377, 1240, 1172, 1143, 1001, 903, 846, 824 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{10}H_{11}O$: 147.0810 observed: 147.0813.

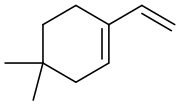
(*E*)-buta-1,3-dien-1-ylcyclohexane (**32e**):



32e

Prepared according to the literature procedure.[56] Analytical data matchs the literature.[56]

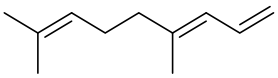
4,4-dimethyl-1-vinylcyclohex-1-ene (**32f**):



32f

Prepared according to the literature procedure.[57] Analytical data matchs the literature.[57]

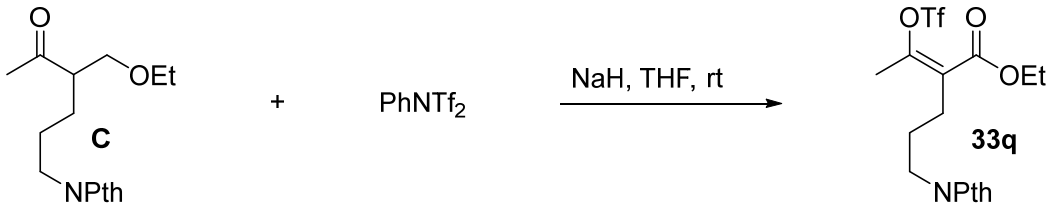
(*E*)-4,8-dimethylnona-1,3,7-triene (**32g**):



32g

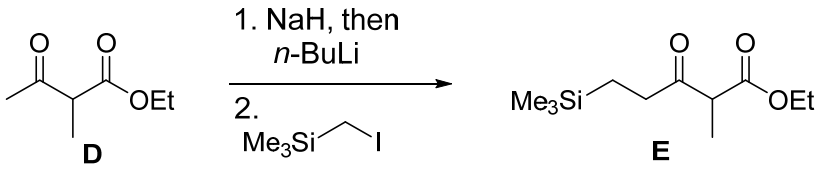
Prepared according to the literature procedure.[58] Analytical data matchs the literature.[58]

Ethyl (*Z*)-5-(1,3-dioxoisoindolin-2-yl)-2-(1-(((trifluoromethyl)sulfonyl)oxy)ethylidene) pentanoate (**33q**):



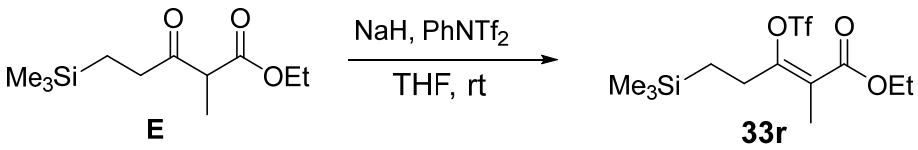
To an oven dried 50 mL round bottom flask, was added 168 mg of NaH (60% dispersion in mineral oil, 5.0 mmol, 1.0 equiv).[38] The flask was purged with N_2 and 15 mL of THF was added. Then 1.6 g of β-keto ester **C** (5.0 mmol, 1.0 equiv), dissolved in 5 mL of THF, was added dropwise. *Caution*: H_2 is evolved during the addition. The reaction mixture was stirred for 15 min followed by addition of 2.0 g of $PhNTf_2$ (5.6 mmol, 1.1 equiv) in one portion. The reaction mixture was stirred for 6 h followed by quenching with 5 mL of water. The reaction mixture was extracted with 1x50 mL of Et_2O, organic layer washed with 1x10 mL of brine, dried over $MgSO_4$, and solvents evaporated under reduced pressure. The product was then purified by flash column chromatography (20→40% Et_2O:hexanes) to afford **33q** as a colorless oil (1.40 g, 62% yield, *Z* isomer); R_f = 0.20 (40% Et_2O:hexane). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.80 (d, *J* = 5.0 Hz, 2H), 7.71 (d, *J* = 5.0 Hz, 2H), 4.20 (q, *J* = 6.7 Hz, 2H), 3.69 (t, *J* = 7.5 Hz, 2H), 2.39 (t, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.84 (quint, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 5.0 Hz, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 168.5, 165.3, 148.6, 134.4, 132.5, 126.3, 123.4, 118.8 (q, $^1J_{CF}$ = 320.9 Hz), 62.1, 37.7, 27.6, 27.4, 17.7, 14.1; ATR-FTIR (neat); 3392, 2933, 2360, 2342, 1772, 1707, 1616, 1513, 1396, 1265, 1214, 1170, 1078, 1036, 886, 733, 720, 702, 668 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{18}H_{18}NO_7NaSF_3$: 472.0654 observed: 472.0662.

Ethyl (*Z*)-2-methyl-3-(((trifluoromethyl)sulfonyl)oxy)-5-(trimethylsilyl)pent-2-enoate (**33r**):



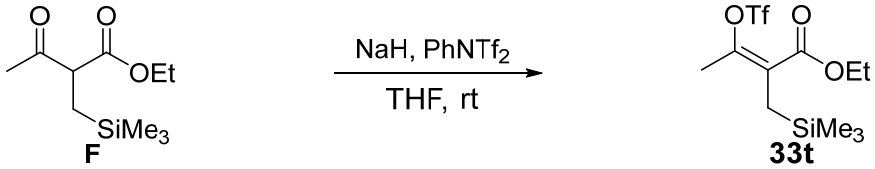
D **E**

To a 1.3 g of NaH (60% dispersion in mineral oil, 39 mmol, 1.3 equiv) was added 60 mL of THF. To this mixture, 4.2 mL of β-keto ester **D** (30 mmol, 1.0 equiv) was added dropwise and the resulting suspension was stirred for 15 min.[59] The reaction mixture was then cooled to 0 °C and 14.4 mL of a *n*-BuLi solution (2.5 M solution in hexanes, 36.0 mmol, 1.2 equiv) was added. After stirring for 30 min at 0 °C, 4.9 mL of (iodomethy)trimethylsilane (33 mmol, 1.1 equiv) was added in one portion. The mixture was allowed to warm to room temperature and stirred for 2 h followed by quenching with 10 mL of 5% H_2SO_4. The organic layer was separated and the aqueous layer was extracted with Et_2O (2x50 mL). The combined organic layers were washed with brine (1x30 mL), dried over $MgSO_4$, and concentrated under vacuum. The product was then purified by flash column chromatography (3→6% EtOAc:hexanes) to afford **E** as a colorless oil (5.0 g, 72% yield); R_f = 0.28 (6% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (q, *J* = 8.3 Hz, 2H), 3.54 (q, *J* = 8.3 Hz, 1H), 2.59-2.36 (m, 2H), 1.33 (d, *J* = 5.0 ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.7, 170.7, 61.3, 52.3, 36.3, 14.2, 13.1, 10.1, -1.8; ATR-FTIR (neat); 2953, 2897, 2360, 2342, 1743, 1715, 1456, 1410, 1376, 1248, 1178, 1070, 832, 755, 691, 668 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{11}H_{22}O_3NaSi$: 253.1236 observed: 253.1233.



The synthesis of **33r** was achieved following the same procedure as that of **33q**, using 1.1 g of β-keto ester **E** (5.0 mmol, 1.0 equiv), 185 mg of NaH (60% dispersion in mineral oil, 5.5 mmol, 1.1 equiv), 2.0 g of $PhNTf_2$ (5.5 mmol, 1.1 equiv) and 10 mL of THF. The product was then purified by flash column chromatography (2→4% EtOAc:hexanes) to afford **33r** as a colorless oil (1.2 g, 67% yield, *Z* isomer); R_f = 0.33 (6% EtOAc:hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (q, *J* = 7.0 Hz, 2H), 2.37 (t, *J* = 9.0 Hz, 2H), 1.97 (s, 3H), 1.32 (t, *J* = 6.0 Hz, 3H), 0.79 (t, *J* = 9.0 Hz, 2H), 0.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 153.6, 120.5, 118.5 (q, $^1J_{CF}$ = 320.5 Hz), 61.8, 26.0, 15.0, 14.0, 13.6, -2.1; ATR-FTIR (neat); 2956, 1723, 1660, 1420, 1247, 1204, 1137, 1098, 1029, 909, 830, 759, 601 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{12}H_{21}O_5NaSSiF_3$: 385.0729 observed: 385.0733.

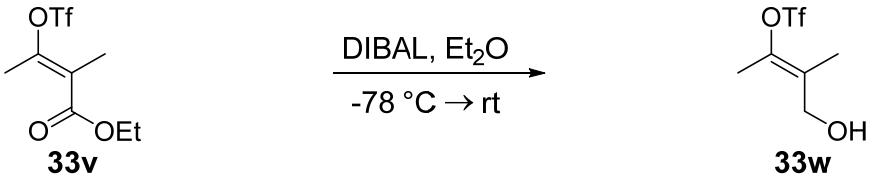
Ethyl (*E*)-3-(((trifluoromethyl)sulfonyl)oxy)-2-((trimethylsilyl)methyl)but-2-enoate (**33t**):



The same procedure as used for the synthesis of **33q** was followed using 1.1 g of β-keto ester **F** (5.0 mmol, 1.0 equiv), 185 mg of NaH (60% dispersion in mineral oil, 5.5 mmol, 1.1 equiv), 2.0 g of $PhNTf_2$ (5.5 mmol, 1.1 equiv) and 10 mL of THF. The product was then purified by flash column chromatography (1→2% EtOAc:hexanes) to afford **33t** as a colorless oil (1.2 g, 70% yield, *Z* isomer); R_f = 0.38 (6% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 (q, *J* = 8.3 Hz, 2H), 2.02 (s, 3H), 1.76 (s, 2H), 1.29 (t, *J* = 7.5

Hz, 3H), 0.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 143.9, 125.7, 122.4, 119.8, 117.3, 114.8, 61.8, 20.2, 17.7, 14.0, -1.3; ATR-FTIR (neat); 2959, 1724, 1419, 1293, 1248, 1203, 1137, 1090, 1037, 925, 835, 693, 609 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{11}H_{19}O_5NaSiSF_3$: 371.0572 observed: 371.0576.

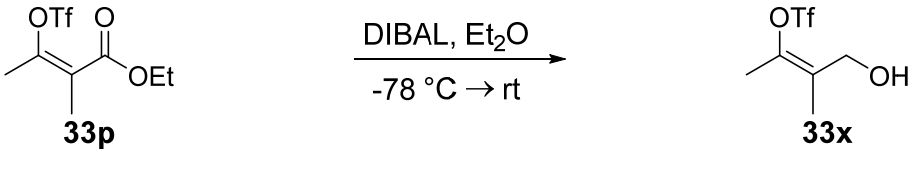
(*E*)-4-hydroxy-3-methylbut-2-en-2-yl trifluoromethanesulfonate (**33w**):



33v **33w**

The representative procedure developed by Meyer and co-workers[44] was followed to synthesize **33w** using 414 mg (1.5 mmol, 1.0 equiv) of **33v**, 2.2 mL of DIBAL-H (25 wt.% in toluene, ≈2.2 equiv) and 10 mL of Et_2O (instead of THF). The product was then purified by flash column chromatography (20→30% Et_2O:hexanes) to afford **33w** as a light yellow oil (286 mg, 81% yield); R_f = 0.16 (30% Et_2O:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (s, 2H), 2.10 (s, 3H), 2.01 (br, 1H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 128.1, 118.5 (q, $^1J_{CF}$ = 317.7 Hz), 62.7, 16.6, 14.6; ATR-FTIR (neat); 3355, 1696, 1408, 1200, 1130, 1084, 1012, 905, 817, 767, 631 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_6H_9O_4NaSF_3$: 257.0071 observed: 257.0074.

(*Z*)-4-hydroxy-3-methylbut-2-en-2-yl trifluoromethanesulfonate (**33x**):

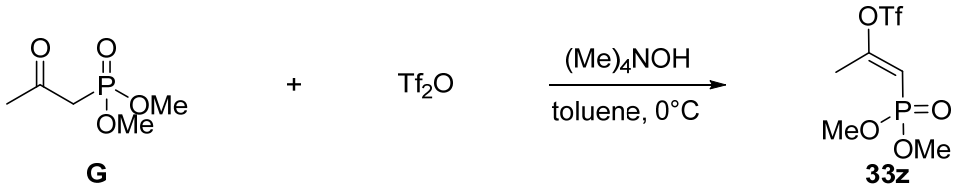


33p **33x**

The general procedure used to synthesize **33w** was employed using 829 mg (3.0 mmol, 1.0 equiv) of **33p**, 4.4 mL of DIBAL-H (25 wt.% in toluene, ≈2.2 equiv) and 20 mL of Et_2O. The product was then purified by flash column chromatography (20→30%

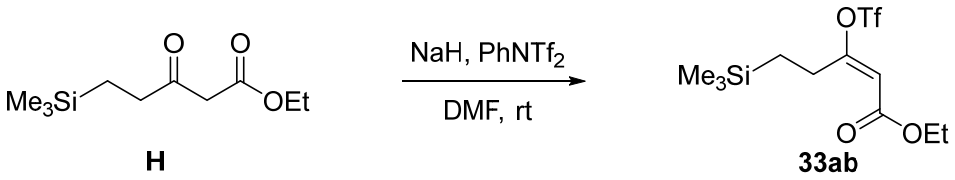
Et_2O:hexanes) to afford **33x** as a light yellow oil (573 mg, 81% yield); R_f = 0.26 (30% Et_2O:hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 2H), 2.05 (s, 4H, -***CH₃*** and –***OH*** overlapping), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 128.4, 118.5 (q, $^1J_{CF}$ = 317.7 Hz), 60.8, 16.7, 15.2; ATR-FTIR (neat); 3355, 1696, 1410, 1203, 1135, 1084, 1012, 905, 817, 767, 631 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_6H_9O_4NaSF_3$: 257.0071 observed: 257.0074.

(*E*)-1-(dimethoxyphosphoryl)prop-1-en-2-yl trifluoromethanesulfonate (**33z**):



The representative procedure developed by Frantz and co-workers[39] for the synthesis of *E*-enol triflates was employed, using 1.28 g of β-keto phosphonate **G** (7.68 mmol, 1.0 equiv), 3.23 mL of Tf_2O (19.2 mmol, 2.5 equiv), 13.8 mL of Me_4NOH (25% solution in H_2O, 38.4 mmol, 5.0 equiv) and 40 mL of toluene. The product was then purified by flash column chromatography (60→80% EtOAc:hexanes) to afford **33z** as a colorless oil (458 mg, 20% yield, *E* isomer); R_f = 0.45 (70% EtOAc:hexanes). The low yield is likely due to product decomposition on the silica gel column.[60] ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 (dd, *J* = 4.25, 0.75 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 2.45 (d, *J* = 2.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (d, *J* = 27.7 Hz), 118.6 (q, *J* = 320.0 Hz), 107.5 (d, *J* = 190.3 Hz), 52.9 (d, *J* = 6.3 Hz), 19.4 (d, *J* = 1.3 Hz); ATR-FTIR (neat); 2959, 1660, 1419, 1244, 1100, 1023, 991, 933, 780, 742, 608 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_6H_{10}O_6NaPSF_3$: 320.9786 observed: 320.9795.

Ethyl (*E*)-3-(((trifluoromethyl)sulfonyl)oxy)-5-(trimethylsilyl)pent-2-enoate (**33ab**):



H **33ab**

To an oven dried 20 mL scintillation vial was added 148 mg of NaH (60% dispersion in mineral oil, 4.4 mmol, 1.1 equiv).[61] The vial was purged with nitrogen and 5 mL of DMF was added. Then 865 mg of β-keto ester **H** (4.0 mmol, 1.0 equiv) dissolved in 1 mL of DMF was added dropwise. *Caution*: H_2 is evolved during the addition. The reaction mixture was stirred for 15 min followed by addition of 1.6 g of $PhNTf_2$ (4.4 mmol, 1.1 equiv) in one portion. The reaction mixture was stirred for 6 h followed by quenching with 5 mL of water. The reaction mixture was extracted with 1x50 mL of Et_2O, organic layer washed with 1x10 mL of brine, dried over $MgSO_4$, and solvents evaporated under reduced pressure. The product was then purified by flash column chromatography (1→2% Et_2O:hexanes) to afford **33ab** as a colorless oil (976 mg, 70% yield, *E* isomer), R_f = 0.51 (2% EtOAc:hexanes). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 5.83 (s, 1H), 4.18 (q, J = 6.7 Hz, 2H), 2.86 (t, J = 7.5 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H), 0.80 (t, J = 7.5 Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 164.2, 118.6 (q, $^1J_{CF}$ = 320.5 Hz), 111.3, 61.2, 26.3, 14.2, 13.7, -2.03; ATR-FTIR (neat); 2957, 2360, 1726, 1662, 1422, 1247, 1204, 1138, 1028, 972, 926, 859, 834, 712, 640 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{11}H_{19}O_5NaSiSF_3$: 371.0572 observed: 371.0574.

General procedure for the optimization of the reaction of 1,3-diene with cyclic enol nonaflate

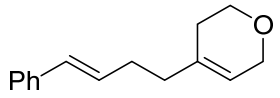
The general procedure A, described below, was used with the following modifications. The reaction was performed on 0.20 mmol scale with ≈ 10 wt% internal standard (2-methoxynapthalene). After work-up the reaction mixture was analyzed for product formation by ^{1}H NMR. The modifications described in Table 4.1 were applied in order to optimize the reaction.

General procedure A for the reaction of 1,3-dienes with cyclic enol nonaflates (or triflates)

To a 4 mL oven dried vial with a stir bar, was added diene (0.5 mmol, 1.0 equiv), vinyl nonaflate/triflate (0.5 mmol, 1.0 equiv), 51.0 mg of sodium formate (0.75 mmol, 1.5 equiv), and 10.4 mg of $Pd_2dba_3 \cdot CHCl_3$ (0.01 mmol, 0.02 equiv). The vial was sealed with a phenolic screw cap fitted with a septa. The vial was then evacuated and filled with nitrogen. This cycle was repeated three times followed by addition of 1.5 mL of DMA via syringe. Further, parafilm was wrapped around the cap to make the vial air tight. The suspension was then allowed to stir at room temperature for 16 h followed by filtration through a plug of silica gel with 20 mL of methy *tert*-butyl ether (MTBE). The solution was transferred to a separatory funnel and further diluted with 30 mL of MTBE and washed with 3x10 mL of water and finally with brine (1x10 mL). The organic layer was dried over anhydrous $MgSO_4$ followed by removal of solvents under reduced pressure. The ^{1}H NMR of the crude reaction mixture was taken at this stage to determine the reported regioselectivity of the reaction. The product was then purified by flash column

chromatography. *Note*: Yields are reported as a mixture of isomers.

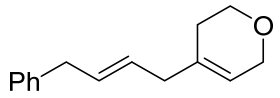
(*E*)-4-(4-phenylbut-3-en-1-yl)-3,6-dihydro-2H-pyran (**34a**):



34a

The general procedure A was followed using 65.0 mg of diene (0.5 mmol, 1.0 equiv) and 191.0 mg of enol nonaflate (0.5 mmol, 1.0 equiv). The product was then purified by flash column chromatography (0→2% EtOAc:hexanes) to afford **34a** as a colorless oil (80 mg, 75% yield, **34a**:**35a**::15:1), R_f = 0.13 (2% EtOAc:hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.18 (m, 5H), 6.42 (d, *J* = 18.0 Hz, 1H), 6.23 (dt, *J* = 18.0, 6.0 Hz, 1H), 5.48 (m, 1H), 4.16-4.12 (m, 2H), 3.81 (t, *J* = 6.0 Hz, 2H), 2.37 (q, *J* = 7.0 Hz, 2H), 2.18 (t, *J* = 7.5 Hz, 2H), 2.12-2.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 135.2, 130.3, 128.6, 127.1, 126.1, 120.2, 65.6, 64.5, 37.0, 31.0, 28.8; ATR-FTIR (neat); 3023, 2921, 2845, 2360, 2342, 1494, 1383, 1126, 962, 849, 741, 691 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{15}H_{19}O$: 215.1436 observed: 215.1434.

(*E*)-4-(4-phenylbut-2-en-1-yl)-3,6-dihydro-2H-pyran (**35a**):

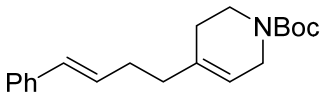


35a

The product is reported as a regioisomer of **34a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H), 5.68-5.58 (m, 1H), 5.53-5.43 (m, 2H), 4.12-4.11 (m, 2H), 3.77 (t, *J* = 4.5 Hz, 2H), 3.36 (d, *J* = 6.0 Hz, 2H), 2.71 (d, *J* = 6.0 Hz, 2H), 2.08-2.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 134.9, 131.4, 128.7 (128.73), 128.7 (128.69), 128.6, 126.2, 120.5, 65.8, 64.6, 40.4, 39.2, 28.7; ATR-FTIR (neat); 3023, 2921, 2845, 2360, 2342,

1494, 1383, 1126, 962, 849, 741, 691; HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{15}H_{19}O$: 215.1436 observed: 215.1434.

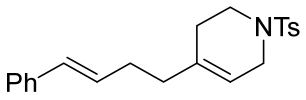
Tert-butyl (*E*)-4-(4-phenylbut-3-en-1-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**34b**):



34b

The general procedure A was followed using 65 mg of diene (0.5 mmol, 1.0 equiv) and 241 mg of enol nonaflate (0.5 mmol, 1.0 equiv). The product was then purified by flash column chromatography (2→4% EtOAc:hexanes) to afford **34b** as a colorless oil (128 mg, 82% yield, 10:1), R_f = 0.42 (10% EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 4H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.38 (d, *J* = 16.0 Hz, 1H), 6.19 (dt, *J* = 16.0, 6.0 Hz, 1H), 5.42-5.35 (m, 1H), 3.89-3.82 (m, 2H), 3.49 (t, *J* = 6.0 Hz, 2H), 2.32 (q, *J* = 6.7 Hz, 2H), 2.16 (t, *J* = 8.0 Hz, 2H), 2.07-2.03 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 155.2, 138.1, 136.3, 130.5, 130.3, 128.7, 127.1, 126.1, 118.6, 79.6, 43.6, 40.6, 37.2, 31.2, 29.9, 28.7; ATR-FTIR (neat); 3380, 2970, 2928, 2360, 2342, 1684, 1419, 1366, 1240, 1163, 1112, 951, 692, 669 cm^{-1}; HRMS (ESI) m/z calculated for $C_{20}H_{27}NO_2Na$: 336.1939 observed 336.1943.

(*E*)-4-(4-phenylbut-3-en-1-yl)-1-tosyl-1,2,3,6-tetrahydropyridine (**34c**):

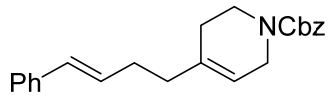


34c

The general procedure A was followed using 65 mg of diene (0.5 mmol, 1.0 equiv) and 268 mg of enol nonaflate (0.5 mmol, 1.0 equiv). The product was then purified by flash column chromatography (5→8% EtOAc:hexanes) to afford **34c** as a white solid (118

mg, 64% yield, 9.1:1), Mp = 137 °C, R_f = 0.23 (10% EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.31-7.25 (m, 7H), 7.19 (t, *J* = 6.0 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.13 (dt, *J* = 16.0, 8.0 Hz, 1H), 5.36-5.34 (m, 1H), 3.56-3.54 (m, 2H), 3.18 (t, *J* = 6.0 Hz, 2H), 2.41 (s, 3H), 2.26 (q, *J* = 8.0 Hz, 2H), 2.16-2.09 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 138.0, 136.3, 134.3, 130.7, 130.0, 129.8, 128.7, 128.0, 127.2, 126.2, 117.2, 45.0, 43.1, 36.9, 31.1, 28.8, 21.7; ATR-FTIR (neat); 2922, 2360, 2342, 1653, 1597, 1473, 1340, 1165, 962, 682, 669 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{22}H_{25}NO_2SNa$: 390.1504 observed: 390.1508.

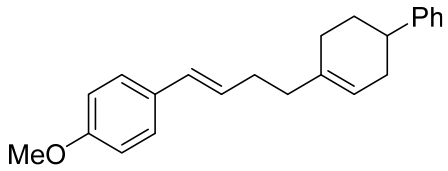
Benzyl (*E*)-4-(4-phenylbut-3-en-1-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**34d**):



34d

The general procedure A was followed using 65 mg of diene (0.5 mmol, 1.0 equiv) and 258 mg of enol nonaflate (0.5 mmol, 1.0 equiv). The product was then purified by flash column chromatography (5→10% EtOAc:hexanes) to afford **34d** as a colorless oil (136 mg, 78% yield, 13.6:1), R_f = 0.17 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.29 (m, 9H), 7.21 (t, *J* = 7.5 Hz, 1H), 6.41 (d, *J* = 15.0 Hz, 1H), 6.21 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.46-5.39 (m, 1H), 5.17 (s, 2H), 3.98-3.96 (m, 2H), 3.62-3.59 (m, 2H), 2.35 (q, *J* = 8.3 Hz, 2H), 2.20-2.10 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 155.7, 138.0, 137.3, 136.4, 130.6, 130.2, 128.7 (128.69), 128.7 (128.66), 128.1 (128.11), 128.1 (128.06), 127.1, 126.2, 118.2, 67.2, 43.6, 40.9, 37.2, 31.2, 28.6; ATR-FTIR (neat); 3025, 2899, 2838, 2360, 2342, 1698, 1420, 1281, 1233, 1105, 963, 742, 694, 668 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{23}H_{26}NO_2$: 348.1964 observed: 348.1969.

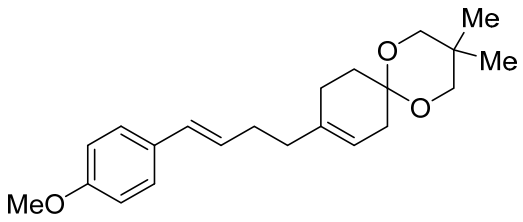
(*E*)-4-(4-(4-methoxyphenyl)but-3-en-1-yl)-1,2,3,6-tetrahydro-1,1'-biphenyl (**34e**):



34e

The general procedure A was followed using 80 mg of diene (0.5 mmol, 1.0 equiv) and 228 mg of enol nonaflate (0.5 mmol, 1.0 equiv). The product was then purified by flash column chromatography (10→20% Benzene:hexanes) to afford **34e** as a colorless oil (110 mg, 69% yield, 10.8:1), R_f = 0.55 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.19 (m, 7H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.38 (d, *J* = 15.0 Hz, 1H), 6.12 (dt, *J* = 15.0, 5.0 Hz, 1H), 5.56-5.54 (m, 1H), 3.82 (s, 3H), 2.81-2.72 (m, 1H), 2.37-2.30 (m, 3H), 2.20-2.07 (m, 5H), 2.00-1.97 (m, 1H), 1.83-1.75 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 147.5, 137.4, 130.9, 129.4, 128.8, 128.5, 127.2, 127.1, 126.1, 121.1, 114.2, 55.5, 40.4, 37.8, 33.7, 31.6, 30.3, 29.2; ATR-FTIR (neat); 2914, 2834, 2400, 2342, 1605, 1510, 1249, 1176, 1029, 969, 847, 700, 669 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{23}H_{26}ONa$: 341.1881 observed: 341.1883.

(*E*)-9-(4-(4-methoxyphenyl)but-3-en-1-yl)-3,3-dimethyl-1,5-dioxaspiro[5.5]undec-8-ene (**34f**):

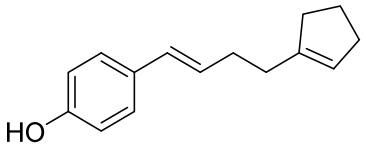


34f

The general procedure A was followed using 80 mg of diene (0.5 mmol, 1.0 equiv)

and 240 mg of enol nonaflate (0.5 mmol, 1.0 equiv). The product was then purified by flash column chromatography (2→4% EtOAc:hexanes) to afford **34f** as a white solid (113 mg, 66% yield, 12:1), Mp = 113 ºC, R_f = 0.33 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.32 (d, *J* = 15.0 Hz, 1H), 6.10-6.04 (m, 1H), 5.32-5.28 (m, 1H), 3.79 (s, 3H), 3.59 (d, *J* = 15.0 Hz, 2H), 3.49 (d, *J* = 15.0 Hz, 2H), 2.38-2.34 (m, 2H), 2.30 (q, *J* = 6.7 Hz, 2H), 2.13-2.08 (m, 4H), 1.97 (t, *J* = 7.5 Hz, 2H), 1.03 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 137.1, 130.8, 129.4, 128.6, 127.2, 117.5, 114.0, 97.5, 70.5, 55.5, 37.0, 35.0, 31.5, 30.5, 27.7, 26.9, 23.1, 22.6; ATR-FTIR (neat); 2953, 2360, 2342, 1772, 1647, 1248, 1113, 669 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{22}H_{30}O_3Na$: 365.2093 observed: 365.2096.

(*E*)-4-(4-(cyclopent-1-en-1-yl)but-1-en-1-yl)phenol (**34g**):

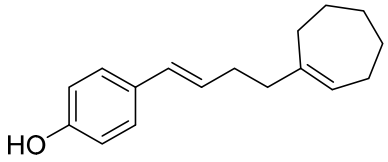


34g

The general procedure A was followed using 73 mg of diene (0.5 mmol, 1.0 equiv) and 183 mg of enol nonaflate (0.5 mmol, 1.0 equiv). The product was then purified by flash column chromatography (5→10% EtOAc:hexanes) to afford **34g** as a white solid (79 mg, 74% yield, 12.6:1), Mp = 62-64 ºC, R_f = 0.19 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 9.0 Hz, 2H), 6.76 (d, *J* =8.5 Hz, 2H), 6.33 (d, *J* = 15.5 Hz, 1H), 6.09 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.39-5.37 (m, 1H), 4.70 (s, 1H), 2.36-2.21 (m, 8H), 1.86 (quint, *J* = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 144.4, 131.2, 129.3, 128.9, 127.4, 123.8, 115.5, 35.4, 32.7, 31.6, 31.4, 23.7; ATR-FTIR (neat); 3423, 2926, 2846, 2360, 2342, 1609, 1511, 1437, 1263, 1171, 963, 734, 703, 668 cm^{-1}; HRMS (ESI)

m/z $(M+H)^+$ calculated for $C_{15}H_{19}O$: 215.1436 observed: 215.1430.

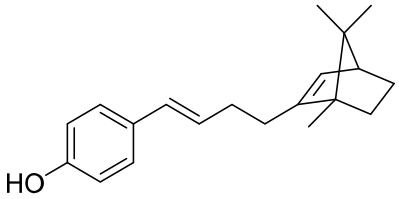
(*E*)-4-(4-(cyclohept-1-en-1-yl)but-1-en-1-yl)phenol (**34h**):



34h

The general procedure A was followed using 73 mg of diene (0.5 mmol, 1.0 equiv) and 197 mg of enol nonaflate (0.5 mmol, 1.0 equiv). The product was then purified by flash column chromatography (10→12% EtOAc:hexanes) to afford **34h** as a white solid (81 mg, 67% yield, 9.7:1), Mp = 68-70 ºC, R_f = 0.23 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.33 (d, *J* = 15.0 Hz, 1H), 6.08 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.59 (t, *J* = 7.5 Hz, 1H), 4.80 (br, 1H), 2.28 (q, *J* = 8.3 Hz, 2H), 2.15-2.07 (m, 6H), 1.74 (quint, *J* = 6.3 Hz, 2H), 1.53-1.45 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 144.3, 131.3, 129.2, 129.0, 127.4, 126.5, 115.6, 40.4, 33.1, 32.9, 32.0, 28.5, 27.6, 27.0; ATR-FTIR (neat); 3317, 2916, 2844, 2360, 2342, 1608, 1510, 1444, 1225, 1169, 961, 842, 738, 668 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{17}H_{23}O$: 243.1749 observed: 243.1749.

4-((*E*)-4-((1R,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)but-1-en-1-yl)phenol (**34i**):

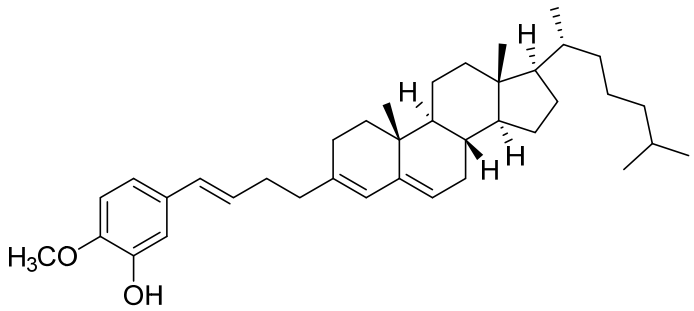


34i

The general procedure A was followed using 73 mg of diene (0.5 mmol, 1.0 equiv) and 142 mg of enol triflate (0.5 mmol, 1.0 equiv). The product was then purified by flash

column chromatography (5→10% EtOAc:hexanes) to afford **34i** as a colorless oil (114 mg, 81% yield, >20:1), R_f = 0.13 (5% EtOAc:hexanes). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 6.34 (d, *J* = 15.0 Hz, 1H), 6.13 (dt, *J* = 15.0, 5.0 Hz, 1H), 5.60 (m, 1H), 5.07 (br, 1H), 2.38-2.27 (m, 2H), 2.23 (t, *J* = 2.5 Hz, 1H), 2.17-2.05 (m, 2H), 1.83 (td, *J* = 7.5, 3.5 Hz, 1H), 1.49 (t, *J* = 8.5 Hz, 1H), 0.98 (s, 3H), 0.95 (d, *J* = 8.0 Hz, 2H), 0.80 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 155.0, 149.4, 131.3, 129.3 (129.29), 129.3 (129.27), 127.5, 126.9, 115.7, 56.6, 54.6, 51.8, 31.7, 31.0, 28.0, 26.4, 19.9 (19.91), 19.9 (19.85), 11.6; ATR-FTIR (neat); 2952, 2360, 2342, 1700, 1653, 1559, 1540, 1511, 1457, 1264, 1171, 966, 733, 703, 669 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{20}H_{27}O$: 283.2062 observed: 283.2075.

5-((*E*)-4-((8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl)but-1-en-1-yl)-2-methoxyphenol (**34j**):

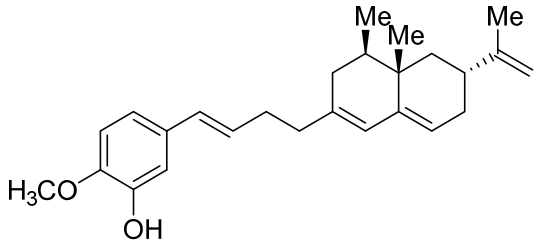


34j

The general procedure A was followed using 53 mg of diene (0.3 mmol, 1.0 equiv), 155 mg of enol triflate (0.3 mmol, 1.0 equiv), 31 mg of sodium formate (0.45 mmol, 1.5 equiv), 6.2 mg of $Pd_2dba_3 \cdot CHCl_3$ (0.006 mmol, 0.02 equiv) and 0.9 mL of DMA. The product was then purified by flash column chromatography (5→10% EtOAc:hexanes) to afford **34j** as a light yellow solid (137 mg, 84% yield, 17.6:1), Mp = 126-129 °C, R_f = 0.24

(10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, *J* = 5.0 Hz, 1H), 6.80-6.76 (m, 2H), 6.29 (d, *J* = 16.0 Hz, 1H), 6.07 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.75 (s, 1H), 5.54 (s, 1H), 5.33-5.32 (m, 1H), 3.87 (s, 3H), 2.33 (q, *J* = 8.3 Hz, 2H), 2.21-2.14 (m, 4H), 2.05-1.97 (m, 3H), 1.86-1.80 (m, 2H), 1.67-1.50 (m, 5H), 1.44-0.97 (m, 15H), 0.93-0.92 (m, 6H), 0.87 (d, *J* = 5.0 Hz, 6H), 0.70 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 145.8, 142.1, 136.4, 132.0, 129.5, 129.2, 124.6, 121.7, 118.5, 111.8, 110.8, 57.2, 56.4, 56.1, 48.6, 42.7, 40.1, 39.8, 37.5, 36.4, 36.0, 35.1, 34.4, 32.1, 32.0, 31.7, 28.5, 28.3, 26.6, 24.4, 24.1, 23.1, 22.8, 21.4, 19.1, 19.0, 12.2; ATR-FTIR (neat); 3350, 2934, 2360, 2342, 1790, 1507, 1456, 1419, 1359, 1220, 1092, 1028, 901, 668 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{38}H_{56}O_2Na$: 567.4178 observed: 567.4189.

5-((*E*)-4-((4R,4aS,6R)-4,4a-dimethyl-6-(prop-1-en-2-yl)-3,4,4a,5,6,7-hexahydronaphthalen-2-yl)but-1-en-1-yl)-2-methoxyphenol (**34k**):

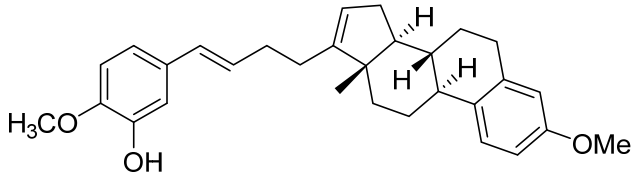


34k

The general procedure A was followed using 53 mg of diene (0.3 mmol, 1.0 equiv), 105 mg of enol triflate (0.3 mmol, 1.0 equiv), 31 mg of sodium formate (0.45 mmol, 1.5 equiv), 6.2 mg of $Pd_2dba_3 \cdot CHCl_3$ (0.006 mmol, 0.02 equiv) and 0.9 mL of DMA. The product was then purified by flash column chromatography (3→6% EtOAc:hexanes) to afford **34k** as a colorless oil (98 mg, 86% yield, 11.5:1), R_f = 0.29 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.80-6.76 (m, 2H), 6.30 (d, *J* = 15.0 Hz, 1H), 6.06 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.78 (s, 1H), 5.38-5.36 (m, 1H), 4.75 (d, *J* = 5.0 Hz, 2H),

3.87 (s, 3H), 2.46-2.40 (m, 1H), 2.33 (q, J = 6.6 Hz, 2H), 2.26-2.15 (m, 3H), 2.00-1.93 (m, 4H), 1.54 (sex, J = 8.3 Hz, 1H), 1.18 (t, J = 12.5 Hz, 1H), 0.91 (d, J = 5.0 Hz, 3H), 0.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 145.9, 145.8, 142.6, 137.2, 131.9, 129.6, 129.1, 124.3, 121.3, 118.5, 111.8, 110.8, 108.7, 56.2, 40.4, 39.3, 37.6, 37.3, 36.1, 35.8, 31.5, 31.4, 20.9, 17.6, 15.0; ATR-FTIR (neat); 3320, 2971, 2874, 2359, 1643, 1584, 1510, 1441, 1381, 1268, 1118, 1030, 962, 884, 792, 760, 733, 640 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{26}H_{34}O_2Na$: 401.2457 observed: 401.2470.

2-methoxy-5-((*E*)-4-((8S,9S,13S,14S)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-17-yl)but-1-en-1-yl)phenol (**34l**):

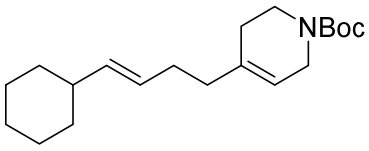


34l

The general procedure A was followed using 53 mg of diene (0.3 mmol, 1.0 equiv) and 125 mg of enol triflate (0.3 mmol, 1.0 equiv), 31 mg of sodium formate (0.45 mmol, 1.5 equiv), 6.2 mg of $Pd_2dba_3 \cdot CHCl_3$ (0.006 mmol, 0.02 equiv) and 0.9 mL of DMA. The product was then purified by flash column chromatography (6→10% EtOAc:hexanes) to afford **34l** as a white solid (93 mg, 70% yield, >20:1), Mp = 110 ºC, R_f = 0.16 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.5 Hz, 1H), 7.00 (d, J = 5.0 Hz, 1H), 6.82-6.77 (m, 2H), 6.72 (dd, J = 7.5, 2.5 Hz, 1H), 6.65 (s, 1H), 6.33 (d, J = 20.0 Hz, 1H), 6.15 (dt, J = 15.0, 5.0 Hz, 1H), 5.57 (s, 1H), 5.40-5.37 (m, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 2.96-2.84 (m, 2H), 2.43-2.15 (m, 6H), 1.96-1.86 (m, 3H), 1.64-1.40 (m, 6H), 0.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.6, 155.4, 146.0, 145.8, 138.3, 133.3, 132.0, 129.5, 129.4, 126.2, 121.7, 118.5, 114.0, 111.7, 111.6, 110.8, 56.6, 56.2, 55.4, 47.2, 44.7,

37.7, 34.9, 31.2, 30.0, 28.1, 27.2, 26.8, 16.1; ATR-FTIR (neat); 3545, 2927, 2838, 2360, 2342, 1635, 1507, 1457, 1266, 1210, 1030, 907, 729 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{30}H_{36}O_3Na$: 467.2562 observed: 467.2570.

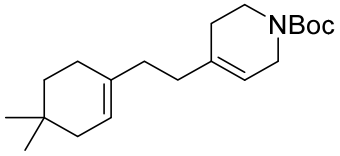
Tert-butyl (*E*)-4-(4-cyclohexylbut-3-en-1-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**34m**):



34m

The general procedure A was followed using 68 mg of diene (0.5 mmol, 1.0 equiv) and 241 mg of enol nonaflate (0.5 mmol, 1.0 equiv). The product was then purified by flash column chromatography (2% EtOAc:hexanes) to afford **34m** as a colorless oil (97 mg, 61% yield, >20:1), R_f = 0.39 (10% EtOAc:hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 5.45-5.29 (m, 3H), 3.85 (m, 2H), 3.47 (m, 2H), 2.67 (d, *J* = 5.0 Hz, 1H), 2.09-2.02 (m, 4H), 1.90 (t, *J* = 7.5 Hz, 1H), 1.69-1.62 (m, 5H), 1.46 (s, 9H), 1.28-1.11 (m, 4H), 1.04 (q, *J* = 11.7, 1H), 0.88 (q, *J* = 11.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, 50 °C) δ 155.2, 137.2, 131.4, 128.2, 127.1, 79.6, 43.6, 40.9, 40.7, 38.3, 37.5, 33.6, 33.4, 30.9, 28.8, 26.9, 26.6, 26.5, 26.3; ATR-FTIR (neat): 2974, 2920, 2849, 2360, 2342, 1696, 1417, 1364, 1237, 1169, 1109, 968, 866, 768, 668 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{20}H_{33}O_2NNa$: 342.2409 observed: 342.2406.

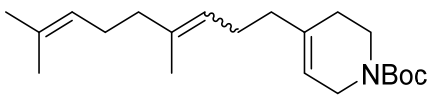
Tert-butyl 4-(2-(4,4-dimethylcyclohex-1-en-1-yl)ethyl)-3,6-dihydropyridine-1(2H)-carboxylate (**34n**):



34n

The general procedure A was followed using 68 mg of diene (0.5 mmol, 1.0 equiv) and 241 mg of enol nonaflate (0.5 mmol, 1.0 equiv). The product was then purified by flash column chromatography (2% EtOAc:hexanes) to afford **34n** as a colorless oil (92 mg, 58% yield, 5.4:1), R_f = 0.39 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32-5.28 (m, 2H), 3.82 (m, 2H), 3.45 (t, *J* = 5.0 Hz, 2H), 2.12-2.03 (m, 6H), 1.92 (t, *J* = 7.5 Hz, 2H), 1.74 (d, *J* = 1.5 Hz, 2H), 1.45 (s, 9H), 1.33 (t, *J* = 5.0 Hz, 2H), 0.86 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 135.9, 120.5, 117.9, 79.5, 41.2, 40.4, 35.9, 35.8, 35.7, 35.1, 33.1, 28.7, 28.4, 26.3, 24.7; ATR-FTIR (neat): 2906, 2833, 2360, 2341, 1697, 1415, 1364, 1286, 1237, 1170, 1108, 986, 866, 769, 668 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{20}H_{33}O_2NNa$: 342.2409 observed: 342.2405.

Tert-butyl 4-(4,8-dimethylnona-3,7-dien-1-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**34o**):



34o

The general procedure A was followed using 75 mg of diene (0.5 mmol, 1.0 equiv) and 241 mg of enol nonaflate (0.5 mmol, 1.0 equiv). The product was then purified by flash column chromatography (2% EtOAc:hexanes) to afford **34o** as a colorless oil (85 mg,

51% yield, 1.8:1), R_f = 0.39 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34-5.30 (m, 1H), 5.10-5.08 (m, 2H), 3.84 (m, 2H), 3.47 (t, *J* = 5.0 Hz, 2H), 2.65 (m, 2H, minor), 2.10-1.91 (m, 10H), 1.67 (s, 3H), 1.59 (s, 6H), 1.46 (s, 9H), 1.28 (q, *J* = 6.7 Hz, 2H, minor), 0.97 (d, *J* = 5.0 Hz, 3H, minor); ^{13}C NMR (126 MHz, $CDCl_3$, 50 °C) δ 155.2, 138.9, 136.8, 135.8, 135.6, 131.7, 131.4, 131.3, 125.5, 125.0, 124.9, 124.6, 124.1, 118.2, 79.5, 43.6, 40.6, 40.0, 37.8, 37.5, 36.6, 32.3, 28.8, 27.1, 26.9, 26.3, 26.2, 26.1, 25.9, 25.8, 23.5, 21.0, 17.9, 16.2; ATR-FTIR (neat): 2972, 2927, 2360, 2342, 1700, 1417, 1352, 1242, 1165, 1141, 968, 861, 768, 668 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{21}H_{35}O_2NNa$: 356.2565 observed: 356.2564.

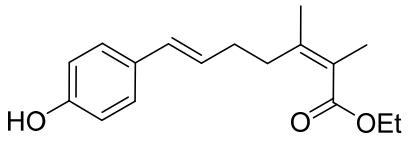
General procedure for the optimization of 1,2-hydrovinylation of 1,3-dienes with *β*-keto ester derived enol triflates

The general procedure B, described below, was used with the following modifications. The reaction was performed on 0.20 mmol scale with ≈ 10 wt% internal standard (2-methoxynapthalene). After work-up, the reaction mixture was analyzed for product formation by ^{1}HNMR. The modifications as described in Table 4.2 were applied in order to optimize the reaction.

General procedure B for 1,2-hydrovinylation of 1,3-dienes with *β*-keto ester derived enol triflates

The general procedure A was followed except 1.3 equiv of enol triflate (0.65 mmol) and 26 mg of $Pd_2dba_3 \cdot CHCl_3$ (0.025 mmol, 0.05 equiv) were used.

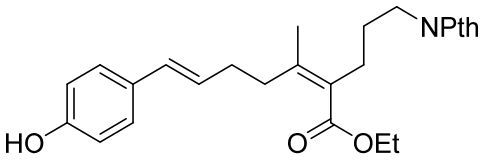
Ethyl (2*Z*,6*E*)-7-(4-hydroxyphenyl)-2,3-dimethylhepta-2,6-dienoate (**34p**):



34p

The general procedure B was followed using 73 mg of diene (0.5 mmol, 1.0 equiv) and 180 mg of enol triflate (0.65 mmol, 1.3 equiv). The product was then purified by flash column chromatography (8→12% EtOAc:hexanes) to afford **34p** as a colorless oil (93 mg, 68% yield, 17:1), R_f = 0.16 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 6.32 (d, *J* = 15.0 Hz, 1H), 6.06 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.01 (br, 1H), 4.18 (q, *J* = 6.7 Hz, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), 2.34 (q, *J* = 6.7 Hz, 2H), 1.86 (s, 3H), 1.82 (s, 3H), 1.29 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 154.9, 145.8, 131.0, 129.5, 128.3, 127.5, 123.6, 115.6, 60.4, 36.6, 32.1, 20.6, 16.1, 14.5; ATR-FTIR (neat); 3382, 2979, 2927, 2359, 1681, 1610, 1512, 1443, 1366, 1271, 1168, 1094, 1022, 964, 837, 773 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{17}H_{22}O_3Na$: 297.1467 observed: 297.1471.

Ethyl (2*Z*,6*E*)-2-(3-(1,3-dioxoisoindolin-2-yl)propyl)-7-(4-hydroxyphenyl)-3-methylhepta-2,6-dienoate (**34q**):

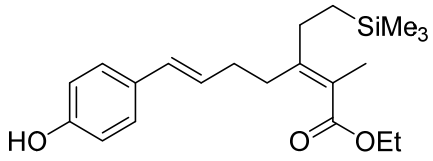


34q

The general procedure B was followed using 44 mg of diene (0.3 mmol, 1.0 equiv), 175 mg of enol triflate (0.39 mmol, 1.3 equiv), 31 mg of sodium formate (0.45 mmol, 1.5 equiv), 16 mg of $Pd_2dba_3{\cdot}CHCl_3$ (0.015 mmol, 0.05 equiv) and 0.9 mL of DMA. The

product was then purified by flash column chromatography (20→30% EtOAc:hexanes) to afford **34q** as a colorless oil (83 mg, 64% yield, 20:1), R_f = 0.17 (30% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.5, 2.5 Hz, 2H), 7.70 (d, *J* = 5.0 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 6.26 (d, *J* = 16.0 Hz, 1H), 6.04-5.97 (m, 2H), 4.14 (q, *J* = 6.7 Hz, 2H), 3.68 (t, *J* = 7.5 Hz, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.29 (q, *J* = 8.3 Hz, 2H), 1.80-1.75 (m, 5H), 1.22 (t, *J* = 5.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 168.6, 155.2, 146.2, 134.1, 132.2, 130.5, 129.6, 127.8, 127.5, 127.4, 123.4, 115.5, 60.5, 38.1, 36.6, 32.0, 27.8, 27.7, 20.1, 14.4; ATR-FTIR (neat); 3380, 2965, 2930, 2360, 2342, 1716, 1700, 1684, 1653, 1559, 1540, 1507, 1457, 669, 650 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{27}H_{29}NO_5Na$: 470.1943 observed: 470.1939.

Ethyl (2*E*,6*E*)-7-(4-hydroxyphenyl)-2-methyl-3-(2-(trimethylsilyl)ethyl)hepta-2,6-dienoate (**34r**):

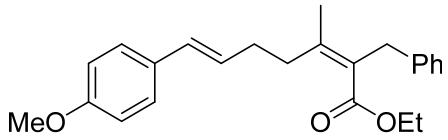


34r

The general procedure B was followed using 73 mg of diene (0.5 mmol, 1.0 equiv) and 236 mg of enol triflate (0.65 mmol, 1.3 equiv). The product was then purified by flash column chromatography (6→12% EtOAc:hexanes) to afford **34r** as a colorless oil (112 mg, 62% yield, 10.2:1), R_f = 0.18 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 5.0 Hz, 2H), 6.32 (d, *J* = 15.0 Hz, 1H), 6.07 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.11 (s, 1H), 4.18 (q, *J* = 6.7 Hz, 2H), 2.50 (t, *J* = 7.5 Hz, 2H), 2.32 (q, *J* = 6.7 Hz, 2H), 2.11-2.07 (m, 2H), 1.86 (s, 3H), 1.29 (t, *J* = 7.5 Hz, 3H), 0.65-0.61 (m, 2H), -0.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 154.9, 153.0, 131.0, 129.4, 128.5,

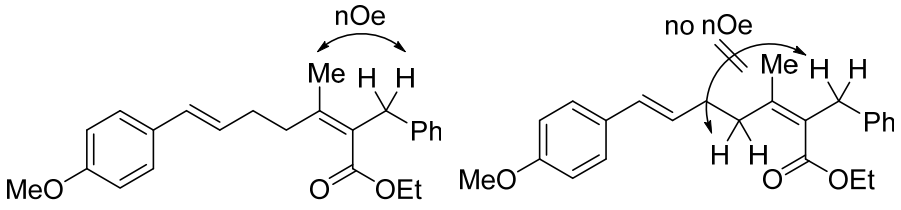
127.5, 122.2, 115.6, 60.4, 34.1, 32.5, 28.1, 15.4, 15.1, 14.5, -1.7; ATR-FTIR (neat); 3390, 2950, 2360, 2342, 1717, 1653, 1510, 1460, 1246, 1170, 1093, 1035, 840, 760, 694, 668 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{21}H_{32}O_3SiNa$: 383.2018 observed 383.2021.

Ethyl (2*Z*,6*E*)-2-benzyl-7-(4-methoxyphenyl)-3-methylhepta-2,6-dienoate (**34s**):



34s

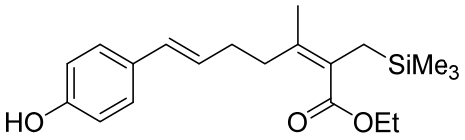
The general procedure B was followed using 80 mg of diene (0.5 mmol, 1.0 equiv) and 229 mg of enol nonaflate (0.65 mmol, 1.3 equiv). The product was then purified by flash column chromatography (3→6% EtOAc:hexanes) to afford **34s** as a colorless oil (91 mg, 50% yield, 9.4:1), R_f = 0.38 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 10.0 Hz, 2H), 7.21-7.14 (m, 5H), 6.84 (d, *J* =9.0 Hz, 2H), 6.36 (d, *J* = 15.0 Hz, 1H), 6.13 (dt, *J* = 16.7, 5.0 Hz, 1H), 4.10 (q, *J* = 8.3 Hz, 2H), 3.81 (s, 3H), 3.70 (s, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.43 (q, *J* = 6.7 Hz, 2H), 1.88 (s, 3H), 1.16 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 158.9, 147.2, 139.9, 130.8, 129.7, 128.5, 128.3, 128.2, 127.6, 127.3, 126.1, 114.1, 60.4, 55.5, 36.5, 35.9, 32.1, 20.5, 14.4; ATR-FTIR (neat); 2926, 2360, 2342, 1709, 1607, 1540, 1437, 1361, 1247, 1220, 1176, 1085, 1032, 967, 846, 735, 700, 668 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{24}H_{28}O_3Na$: 387.1936 observed: 387.1935.



34s

Through-space $^{1}H–^{1}H$ interactions present within **34s** were obtained using a 1D nOe NMR experiment in $CDCl_3$ (500 MHz). The benzyl peak at 3.70 ppm was irradiated and a substantial nOe was observed at the methyl protons (1.87 ppm). This result assigns the *Z*-configuration of tetrasubstituted alkene in **34s**.

Ethyl (2*E*,6*E*)-7-(4-hydroxyphenyl)-3-methyl-2-((trimethylsilyl)methyl)hepta-2,6-dienoate (**34t**):

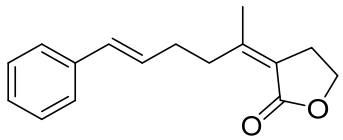


34t

The general procedure B was followed using 73 mg of diene (0.5 mmol, 1.0 equiv) and 226 mg of enol triflate (0.65 mmol, 1.3 equiv). The product was then purified by flash column chromatography (6→12% EtOAc:hexanes) to afford **34t** as a colorless oil (47 mg, 27% yield, 10.3:1), R_f = 0.18 (10% EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 12.0 Hz, 2H), 6.31 (d, *J* = 16.0 Hz, 1H), 6.08 (dt, *J* = 16.0, 8.0 Hz, 1H), 4.98 (br, 1H), 4.16 (q, *J* = 8.0 Hz, 2H), 2.45 (t, *J* = 6.0 Hz, 2H), 2.35 (q, *J* = 6.7 Hz, 2H), 1.81 (s, 2H), 1.74 (s, 3H), 1.29 (t, *J* = 6.0 Hz, 3H), -0.01 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 154.8, 140.5, 131.1, 129.4, 128.5, 127.4, 126.5, 115.5, 60.4, 36.6, 32.5, 20.7 (20.74), 20.7 (20.65), 14.5, -0.9; ATR-FTIR (neat); 3392, 2953, 2360, 2343, 1708, 1612, 1512, 1445, 1368, 1246, 1169, 1097, 1032, 838, 757, 692, 668 cm^{-1};

HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{20}H_{30}O_3SiNa$: 369.1862 observed: 369.1868.

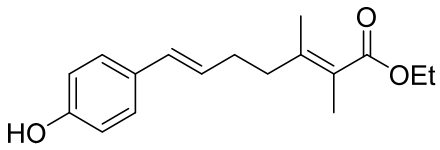
(*Z*)-3-((*E*)-6-phenylhex-5-en-2-ylidene)dihydrofuran-2(3H)-one (**34u**):



34u

The general procedure B was followed using 65 mg of diene (0.5 mmol, 1.0 equiv) and 169 mg of enol triflate (0.65 mmol, 1.3 equiv). The product was then purified by flash column chromatography (6→10% EtOAc:hexanes) to afford **34u** as a colorless oil (70 mg, 58% yield, 11.6:1), R_f = 0.50 (25% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.27 (m, 4H), 7.19 (t, *J* = 7.5 Hz, 1H), 6.40 (d, *J* = 15.0 Hz, 1H), 6.25 (dt, *J* = 15.0, 5.0 Hz, 1H), 4.28 (t, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.39 (q, *J* = 6.7 Hz, 2H), 1.90 (t, *J* = 1.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 153.6, 137.8, 130.6, 130.0, 128.7, 127.1, 126.2, 119.3, 64.4, 32.6, 32.0, 30.0, 22.8; ATR-FTIR (neat); 3024, 2919, 2854, 2360, 2342, 1735, 1654, 1550, 1521, 1447, 1374, 1264, 1195, 1162, 1061, 1035, 966, 744, 694, 668, 655 cm^{-1}; HRMS (ESI) m/z calculated for $C_{16}H_{18}O_2Na$: 265.1204 observed: 265.1201.

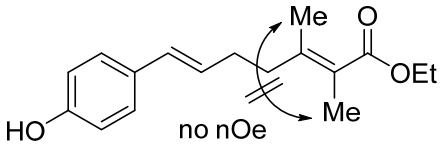
Ethyl (2*E*,6*E*)-7-(4-hydroxyphenyl)-2,3-dimethylhepta-2,6-dienoate (**34v**):



34v

The general procedure B was followed using 73 mg of diene (0.5 mmol, 1.0 equiv) and 180 mg of enol triflate (0.65 mmol, 1.3 equiv). The product was then purified by flash column chromatography (5→10% EtOAc:hexanes) to afford **34v** as a colorless oil (82 mg,

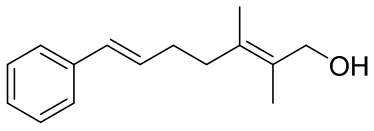
60% yield, **34v**:**35v**::>20:1, **34v**:**34p**::6.6:1), R_f = 0.16 (10% EtOAc:hexanes). *Note*: The selectivity of **34v** vs **34p** was determined using ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.34 (d, *J* = 16.0 Hz, 1H), 6.09-6.02 (m, 1H), 5.46 (br, 1H), 4.20 (q, *J* = 8.0 Hz, 2H), 2.50 (t, *J* = 8.0 Hz, 2H, minor), 2.34 (q, *J* = 6.0 Hz, 2H, minor), 2.29 (br, 4H), 2.02 (d, *J* = 1.2 Hz, 3H), 1.89 (d, *J* = 1.6 Hz, 3H), 1.86 (s, 3H, minor), 1.82 (s, 3H, minor), 1.31 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) major δ 170.3, 155.1, 145.6, 130.8, 130.0, 127.7, 127.5, 123.5, 115.6, 60.4, 36.3, 31.0, 21.2, 15.6, 14.5; Minor δ 170.1, 154.9, 145.7, 131.0, 129.5, 128.3, 127.5, 123.6, 115.6, 60.4 (overlapping), 36.6, 32.1, 20.6, 16.1, 14.5; ATR-FTIR (neat); 3382, 2979, 2927, 2359, 1681, 1610, 1512, 1443, 1366, 1271, 1168, 1094, 1022, 964, 837, 773 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{17}H_{22}O_3Na$: 297.1467 observed: 297.1471.



34v

Through-space ^{1}H–^{1}H interactions present within **34v** were obtained using a 1D nOe NMR experiment in $CDCl_3$ (500 MHz). The methyl peak at 2.02 ppm was irradiated and no substantial nOe was observed upon the other methyl protons (1.89 ppm). This result, and comparison of the ^{1}HNMR of **34p** and **34v**, assigns the *E*-configuration of tetrasubstituted alkene in **34v**.

(2*E*,6*E*)-2,3-dimethyl-7-phenylhepta-2,6-dien-1-ol (**34w**):



34w

The general procedure B was followed using 83 mg of diene (0.64 mmol, 1.0 equiv), 195 mg of enol triflate (0.83 mmol, 1.3 equiv), 65 mg of sodium formate (0.96 mmol, 1.5 equiv), 33 mg of $Pd_2dba_3 \cdot CHCl_3$ (0.015 mmol, 0.05 equiv) and 2.0 mL of DMA. The product was then purified by flash column chromatography (8→12% EtOAc:hexanes) to afford **34w** as a colorless oil (92 mg, 66% yield, 9.6:1), R_f = 0.12 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.28 (m, 4H), 7.20 (t, *J* = 7.5 Hz, 1H), 6.41 (d, *J* = 15.0 Hz, 1H), 6.23 (dt, *J* = 15.0, 7.5 Hz, 1H), 4.14 (s, 2H), 2.31 (q, *J* = 6.7 Hz, 2H), 2.24 (t, *J* = 7.5 Hz, 2H), 1.79 (s, 3H), 1.78 (s, 3H), 1.29 (br, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9, 132.5, 130.5, 130.2, 128.7, 127.1, 126.1, 64.2, 34.9, 31.5, 18.2, 16.5; ATR-FTIR (neat); 3327, 3024, 2921, 2860, 1494, 1446, 1372, 1239, 1071, 994, 961, 741, 714, 694 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{15}H_{20}ONa$: 239.1412 observed: 239.1413.

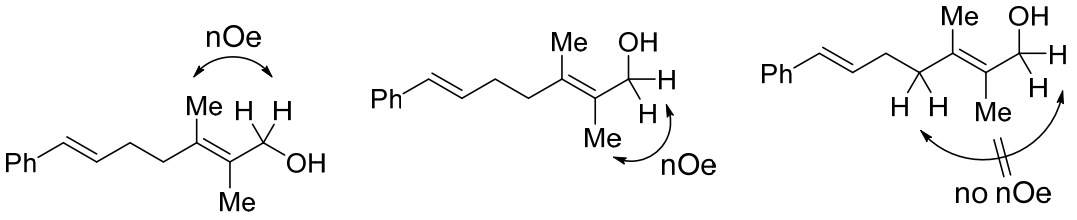


Fig. 4.1

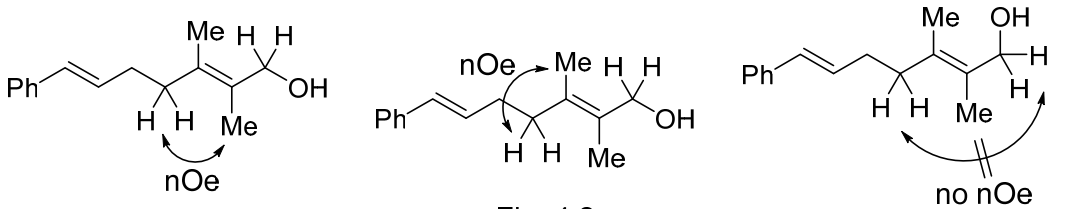


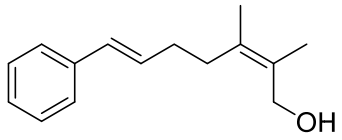
Fig. 4.2

34w

Through-space ^{1}H–^{1}H interactions present within **34w** were obtained using a 1D nOe NMR experiment in $CDCl_3$ (500 MHz). The allylic peak at 4.14 ppm was irradiated and a substantial nOe was observed at the methyl protons (1.78 and 1.79 ppm, Fig. 4.1). However, the allylic protons at 2.24 ppm were unaffected. Similarly, the irradiation of

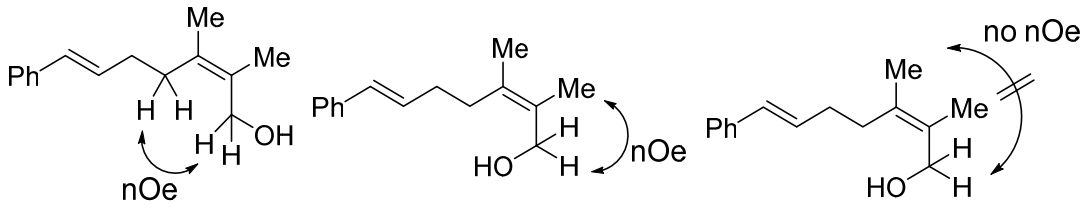
allylic peak at 2.24 ppm led to a substantial nOe of methyl protons (1.78 and 1.79 ppm), whereas allylic protons at 4.14 ppm remained unaffected (Fig. 4.2). This result, and comparison of the ^{1}H NMR of **34w** and **34x**, assigns the *E*-configuration of tetrasubstituted alkene in **34w**.

(2*Z*,6*E*)-2,3-dimethyl-7-phenylhepta-2,6-dien-1-ol (**34x**):



34x

The general procedure B was followed using 65 mg of diene (0.5 mmol, 1.0 equiv) and 152 mg of enol triflate (0.65 mmol, 1.3 equiv). The product was then purified by flash column chromatography (8→12% EtOAc:hexanes) to afford **34x** as a colorless oil (73 mg, 67% yield, 9:1), R_f = 0.18 (10% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (m, 4H), 7.19 (t, *J* = 7.5 Hz, 1H), 6.38 (d, *J* = 15.0 Hz, 1H), 6.22-6.16 (m, 1H), 4.12 (s, 2H), 2.29 (s, 4H), 1.76 (s, 3H), 1.73 (s, 3H), 1.10 (br, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 132.6, 130.6, 130.4, 128.9, 128.8, 127.2, 126.1, 63.8, 34.2, 32.5, 19.1, 16.9; ATR-FTIR (neat); 3329, 3024, 2921, 2860, 2360, 2342, 1495, 1447, 1373, 995, 962, 742, 714, 693, 668 cm^{-1}; HRMS (ESI) m/z calculated for $C_{15}H_{20}ONa$: 239.1412 observed: 239.1413.

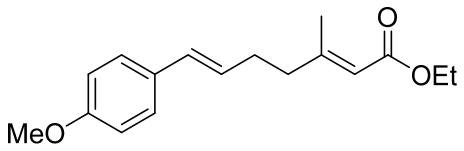


34x

Through-space ^{1}H–^{1}H interactions present within **34x** were obtained using a 1D nOe NMR experiment in $CDCl_3$ (500 MHz). The allylic peak at 4.12 ppm was irradiated

and a substantial nOe was observed upon the other allylic protons (1.76 and 2.29 ppm). This result, and comparison of the ^{1}H NMR of **34w** and **34x**, assigns the *Z*-configuration of tetrasubstituted alkene in **34x**.

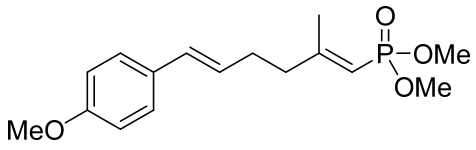
Ethyl (2*E*,6*E*)-7-(4-methoxyphenyl)-3-methylhepta-2,6-dienoate (**34y**):



34y

The general procedure B was followed using 80 mg of diene (0.5 mmol, 1.0 equiv) and 170 mg of enol triflate (0.65 mmol, 1.3 equiv). The product was then purified by flash column chromatography (6→10% EtOAc:hexanes) to afford **34y** as a colorless oil (77 mg, 56% yield, 13:1), R_f = 0.42 (20% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.36 (d, *J* = 15.0 Hz, 1H), 6.03 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.71 (s, 1H), 4.15 (q, *J* = 6.7 Hz, 2H), 3.80 (s, 3H), 2.38 (q, *J* = 6.7 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.19 (d, *J* = 1.5 Hz, 3H), 1.28 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 159.3, 159.0, 130.5, 130.2, 127.3, 127.1, 116.2, 114.1, 59.8, 55.4, 41.0, 31.1, 19.1, 14.6; ATR-FTIR (neat); 2940, 2360, 2342, 1734, 1717, 1700, 1653, 1559, 1540, 1521, 1457, 668, 655 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{17}H_{22}O_3Na$: 297.1467 observed: 297.1469.

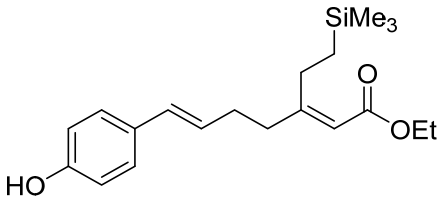
Dimethyl ((1*E*,5*E*)-6-(4-methoxyphenyl)-2-methylhexa-1,5-dien-1-yl)phosphonate (**34z**):



34z

The general procedure B was followed using 80 mg of diene (0.5 mmol, 1.0 equiv) and 194 mg of enol triflate (0.65 mmol, 1.3 equiv). The product was then purified by flash column chromatography (70→90% EtOAc:hexanes) to afford **34z** as a colorless oil (98 mg, 63% yield, 12:1), R_f = 0.17 (70% EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.35 (d, *J* = 15.0 Hz, 1H), 6.01 (dt, *J* = 16.7, 7.5 Hz, 1H), 5.39 (d, *J* = 18.5 Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 2.40-2.31 (m, 4H), 2.12 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4 (d, *J* = 5.0 Hz), 159.0, 130.4, 130.37 (d, *J* = 2.5 Hz), 127.3, 126.8, 114.1, 110.7 (d, *J* = 195.3 Hz), 55.5, 52.2, 41.5 (d, *J* = 22.7 Hz), 31.0, 20.4 (d, *J* = 6.3 Hz); ATR-FTIR (neat); 2950, 2360, 2342, 1707, 1653, 1510, 1457, 1419, 1362, 1243, 1175, 1026, 829, 669, 572 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{16}H_{23}O_4PNa$: 333.1232 observed: 333.1227.

Ethyl (2Z,6E)-7-(4-hydroxyphenyl)-3-(2-(trimethylsilyl)ethyl)hepta-2,6-dienoate (**34ab**):



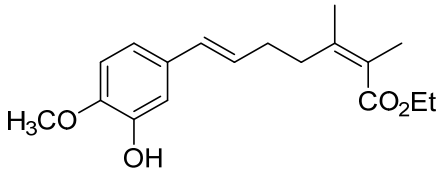
34ab

The general procedure B was followed using 44 mg of diene (0.3 mmol, 1.0 equiv), 136 mg of enol triflate (0.39 mmol, 1.3 equiv), 31.0 mg of sodium formate (0.45 mmol, 1.5 equiv), 16 mg of $Pd_2dba_3 \cdot CHCl_3$ (0.015 mmol, 0.05 equiv) and 0.9 mL of DMA. The product was then purified by flash column chromatography (8→12% EtOAc:hexanes) to afford **34ab** as a colorless oil (67 mg, 67% yield, 9.4:1), R_f = 0.13 (10% EtOAc:hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.35 (d, *J* = 15.0 Hz, 1H), 6.04 (dt, *J* = 14.0, 6.0 Hz, 1H), 5.61 (s, 1H), 5.08 (br, 1H), 4.15 (q, *J* =

8.0 Hz, 2H), 2.61-2.56 (m, 2H), 2.37-2.29 (m, 4H), 1.28 (t, J = 7.5 Hz, 3H), 0.71-0.65 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 166.4, 155.1, 130.6, 130.1, 127.5, 127.2, 115.6, 114.4, 59.8, 37.3, 31.3, 26.5, 16.1, 14.6, -1.6; ATR-FTIR (neat); 3330, 2920, 2359, 2342, 1717, 1700, 1684, 1653, 1647, 1636, 1559, 1541, 1521, 1507, 1457, 668, 665 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{20}H_{30}O_3SiNa$: 369.1862 observed: 369.1866.

Procedure for scale up

Ethyl (2*Z*,6*E*)-7-(4-((l1-oxidanyl)-l5-methyl)-3-hydroxyphenyl)-2,3-dimethylhepta-2,6-dienoate (**34p'**):



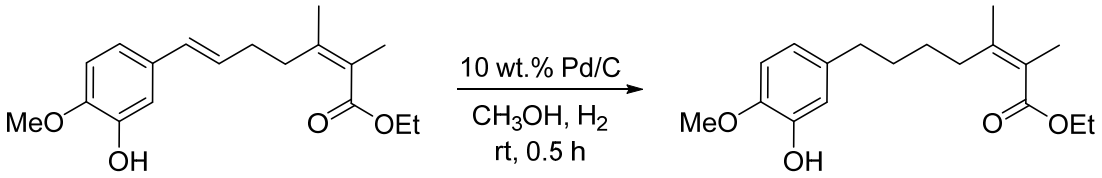
34p'

To a 20 mL oven dried vial with a stir bar, was added 1.2 g of diene **32c** (7.0 mmol, 1.0 equiv), 2.5 g of enol triflate **33p** (9.1 mmol, 1.3 equiv), 714 mg of sodium formate (10.5 mmol, 1.5 equiv), 362 mg of $Pd_2dba_3 \cdot CHCl_3$ (0.35 mmol, 0.05 equiv) and 7.0 mL of DMA. The vial was sealed under nitrogen atmosphere with a phenolic screw cap. Further, parafilm was wrapped around the cap to make the vial air tight. The suspension was then allowed to stir at room temperature for 16 h followed by filtration through a plug of silica gel with 20 mL of methy *tert*-butyl ether (MTBE). The solution was transferred to a separatory funnel and further diluted with 100 mL of MTBE and washed with 3x25 mL of water and finally with brine (1x25 mL). The organic layer was dried over anhydrous $MgSO_4$ followed by removal of solvents under reduced pressure. The ^{1}H NMR of the

crude reaction mixture was taken at this stage to determine the reported regioselectivity of the reduction. The product was then purified by flash column chromatography (6→10% EtOAc:hexanes) to afford **34p'** as a yellow oil (1.6 g, 75% yield, **34p'**:**35p'**::16:1), R_f = 0.12 (10% EtOAc:hexanes). *Note*: Yields are reported as a mixture of isomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.78 (q, *J* = 8.3 Hz, 2H), 6.29 (d, *J* = 15.0 Hz, 1H), 6.08 (dt, *J* = 12.5, 6.3 Hz, 1H), 5.69 (d, *J* = 4.0 Hz, 1H), 4.18 (q, *J* = 6.7 Hz, 2H), 3.85 (s, 3H), 2.50 (t, *J* = 7.5 Hz, 2H), 2.34 (q, *J* = 6.7 Hz, 2H), 1.86 (s, 3H), 1.81 (s, 3H), 1.29 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 145.9, 145.8, 145.5, 131.8, 129.5, 128.8, 123.6, 118.4, 111.8, 110.7, 60.3, 56.1, 36.5, 32.1, 20.5, 16.0, 14.5; ATR-FTIR (neat): 3430, 2934, 2840, 1701, 1584, 1509, 1440, 1267, 1211, 1162, 1094, 1026, 963, 869, 760, 609 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{18}H_{24}O_4Na$: 327.1572 observed: 327.1570.

Procedure for the selective reduction of **34p'**

Ethyl (*Z*)-7-(4-((l1-oxidanyl)-l5-methyl)-3-hydroxyphenyl)-2,3-dimethylhept-2-enoate (**36**):

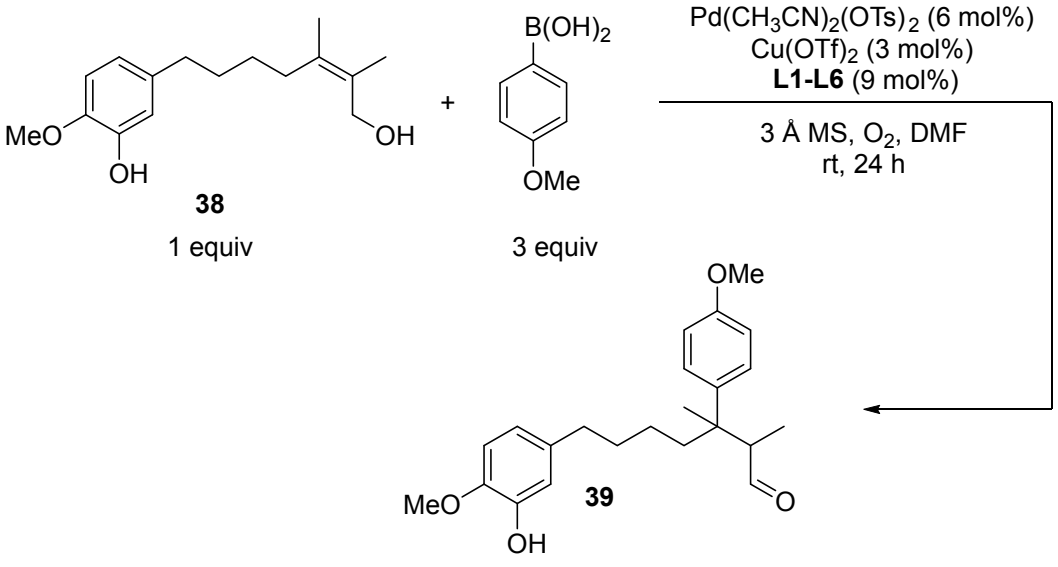


34p' **36**, 99% yield

To a 20 mL oven dried Schlenk flask with a stir bar, was added 700 mg of **34p'** (2.3 mmol, 1.0 equiv), 8.6 mg of 10 wt. % Pd on activated carbon (0.008 mmol, 3.7 mg/mmol). The flask was connected to a three way adapter fitted with a hydrogen balloon on one end. The flask was evacuated and filled with hydrogen and the process was repeated

three times. To the flask, 15 mL of MeOH was added, and the suspension was allowed to stir at room temperature for 30 min followed by filtration through a plug of silica gel with 10 mL of methy *tert*-butyl ether (MTBE). The solvents were evaporated under reduced pressure to afford **36** as a colorless oil (698 mg, 99% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (d, *J* = 8.5 Hz, 2H), 6.64 (dd, *J* = 8.5, 2.0 Hz, 1H), 5.68 (s, 1H), 4.17 (q, *J* = 6.7 Hz, 2H), 3.84 (s, 3H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.84 (s, 3H), 1.75 (d, *J* = 1.0 Hz, 3H), 1.59 (quint, *J* = 7.5 Hz, 2H), 1.48 (quint, *J* = 7.5 Hz, 2H), 1.28 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 146.2, 145.6, 144.8, 136.2, 123.0, 119.8, 114.8, 110.7, 60.2, 56.1, 36.3, 35.3, 31.7, 28.1, 20.2, 16.0, 14.4; ATR-FTIR (neat): 3447, 2932, 2857, 2360, 2342, 1700, 1590, 1509, 1442, 1270, 1208, 1091, 1027, 799, 760, 736, 668 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$ calculated for $C_{18}H_{26}O_4Na$: 329.1729 observed: 329.1733.

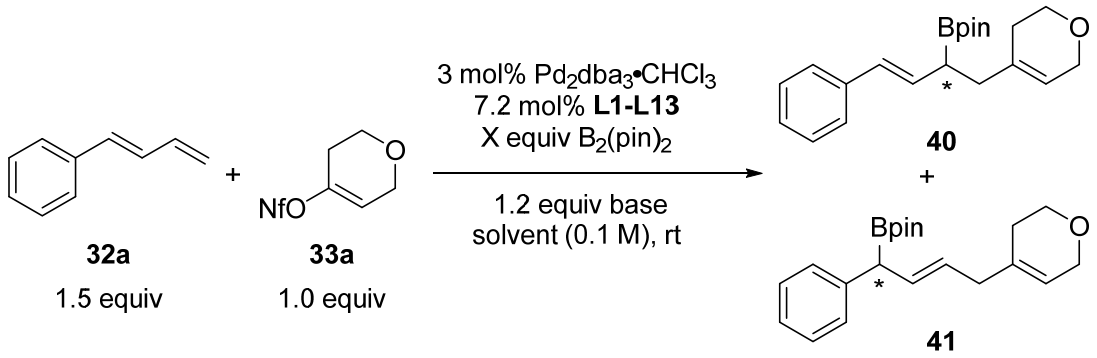
<u>Procedure for the enantioselective Heck reaction on tetrasubstituted alkenol</u>



Reported procedure[47] was followed using 26 mg of **38** (0.1 mmol, 1.0 equiv), 46 mg of *para*methoxyphenyl boronic acid (0.3 mmol, 3.0 equiv), 3.2 mg of $Pd(CH_3CN)_2(OTs)_2$ (0.006 mmol, 0.06 equiv), 1.1 mg of $Cu(OTf)_2$ (0.003 mmol, 0.03 equiv), ligand (0.009 mmol, 0.09 equiv), 15 mg of 3 Å MS, 1 mL of DMF and oxygen balloon. After 36 h, the reaction mixture was filtered through a silica gel plug while eluting with 10 mL of Et_2O followed by further dilution with 10 mL of Et_2O. The filtrate was worked up with H_2O (3x10 mL), followed by washing with brine (1x10 mL). The organic layer was dried using anhydrous $MgSO_4$ followed by evaporation of solvents under reduced pressure. The crude reaction mixture was purified by flash column chromatography (10→12% EtOAc:hexanes) to give compound **39** in 25% (9.2 mg, 0.025 mmol) and 29% (10.9 mg, 0.029 mmol) yields, when **L1** and **L3** ligands were used, respectively (see Figure 4.11). R_f = 0.43 (30% EtOAc:hexanes). *Note:* The yields were not determined with any other ligand. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (d, *J* = 3.3 Hz, 1H), 7.16 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.74-6.68 (m, 2H), 6.56 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.52 (s, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 2.63-2.55 (m, 1H), 2.44-2.33 (m, 2H), 1.94 (td, *J* = 14.2, 4.2 Hz, 1H), 1.71-1.44 (m, 5H), 1.35 (s, 3H), 0.82 (d, J = 6.9 Hz, 3H). The pure compound was reduced with $NaBH_4$ (2.0 equiv) in CH_3OH (approx. 2.0 mL/0.1 mmol scale of the Heck reaction) at 0 °C for 0.5 h. The reaction was quenched with 0.5 mL of water at 0 °C and the mixture was allowed to warm to rt. CH_3OH was evaporated under reduced pressure and the reaction mixture was diluted with 10 mL of Et_2O followed by washing with H_2O (3x5 mL) and finally with brine (1x10 mL). The reaction mixture was dried over anhydrous $MgSO_4$ followed by evaporation of solvents under reduced pressure. The dried compound was dissolved in CH_3OH and chiral

separation was obtained on SFC using column AY-H, ISO 15% *i*-PrOH, 4 mL/min, 40 °C, 160 bar, 6.9 and 8.3 min. The results have been described in Figure 4.11.

General procedure for the optimization of vinylborylation of 1,3-diene



To a 4 mL oven dried vial with a stir bar, was added 39 mg of **32a** (0.3 mmol, 1.5 equiv), 76 mg of **33a** (0.2 mmol, 1.0 equiv), B_2pin_2 (see Table 4.3 for variation), 6.2 mg of $Pd_2dba_3 \cdot CHCl_3$ (0.006 mmol, 0.03 equiv), base (0.24 mmol, 1.2 equiv), and ligand (0.014 mmol, .072 equiv). All the variations described in Table 4.3 and Figure 4.13 were applied in order to optimize the reaction. The vial was sealed with a phenolic screw cap fitted with a septa. The vial was then evacuated and filled with nitrogen. This cycle was repeated three times followed by addition of 1 mL of solvent via syringe. Further, parafilm was wrapped around the cap to make the vial air tight. The suspension was then allowed to stir at room temperature for the desired time followed by filtration through a plug of silica gel with 5 mL of Et_2O. Known amount of 2-methylnapthalene (internal standard) was added to the filtrate and mixed thoroughly. An aliquot was taken out and transferred to a GC vial followed by analysis via GC. The reported regioselectivities are determined via GC trace taken at this point. After GC analysis the aliquot in the GC vial was mixed to the original reaction mixture and then transferred to a separatory funnel and further diluted with 20 mL

of Et_2O and washed with 3x10 mL of water and finally with brine (1x10 mL). *Note:* The work up was skipped when DMA was not used as a solvent. The organic layer was dried over anhydrous $MgSO_4$ followed by removal of solvents under reduced pressure. The product **40** was then purified by silica gel flash column chromatography (5→10% EtOAc:hexanes). R_f = 0.14 (10% EtOAc:hexanes). Isolated yields were not determined because the compound **40** was contaminated by B_2pin_2 impurity even after column chromatography. However, the ^1H and ^{13}C NMR are reported here. ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.0 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.18 (tt, *J* = 7.3, 1.3 Hz, 1H), 6.39 (d, *J* = 15.5 Hz, 1H), 6.2 (dd, *J* = 15.5, 8.0 Hz, 1H), 5.50-5.46 (m, 1H), 4.10-4.08 (m, 2H), 3.76 (t, *J* = 5.5 Hz, 2H), 2.40-2.34 (m, 1H), 2.29-2.20 (m, 2H), 2.15-2.04 (m, 2H), 1.23 (d, *J* = 4.0 Hz, 12H). Peak at 1.27 ppm is probably due to the remaining B_2pin_2. ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 135.2, 131.3, 129.4, 128.6, 126.8, 126.1, 120.5, 83.6, 65.6, 64.5, 38.3, 28.8, 25.2, 24.9, 24.8. One peak out of 24.9 and 24.8 ppm is that of remaining B_2pin_2. The compound **40** was then oxidized to convert allyl Bpin to allyl alcohol in order to determine the enantioselectivity. To 50 mg of compound **40** (containing some B_2pin_2 impurity) was added 3 mL of THF and cooled down to 0 °C. To the solution was added approx. 0.4 mL of 1 M NaOH solution in H_2O dropwise. After stirring for 5 min approx. 0.4 mL of H_2O_2 (30% w/w in water) solution was added dropwise and reaction was stirred at 0 °C. After 1 h the reaction was quenched with 2 mL of saturated solution of $Na_2S_2O_3$ dropwise. *Caution:* Gas is evolved during the addition of $Na_2S_2O_3$. The reaction mixture was diluted with 10 mL of Et_2O, transferred to a separatory funnel, washed with water (1x5 mL) and brine (1x5 mL). The solution was dried over anhydrous $MgSO_4$ and solvents were removed under reduced pressure. Another purification was not

performed at this stage and the dried compound was dissolved in some methanol and aliquot was transferred to GC vial for analysis on SFC. SFC conditions: AY-H column, 2-20% *i*-PrOH for 20 min, 40 ^{o}C, 160 bar, 14.8 and 16.9 minutes.

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